The Instituto Cajal is a neuroscience research center of the Spanish Research Council (CSIC). The Instituto Cajal is the oldest neurobiology research center in Spain. Along its more than 100 years of existence, renowned scientists and professionals trained at the Instituto Cajal have spread worldwide and contributed to the remarkable advancement of neurobiology. Today, the institute is prepared to confront the future challenges and to maintain the leading role in neurobiological research in Spain, always keeping in mind that the final destination of knowledge is the wellbeing of the society.

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2019 CajalXmas Meeting
20 December, 2019

Instituto Cajal, CSIC

With the collaboration of:

BIOCAT
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ReSorchestrating the hippocampal neuronal orchestra in mouse models of schizophrenia and epilepsy

In physiological conditions, cognitive functions normally handled by the hippocampus are encoded by the precise and coordinated firing of the excitatory neurons, which is orchestrated by the activity of specific subpopulations of inhibitory neurons. More specifically, Parvalbumin (PV) and Somatostatin (SOM) interneurons modulate oscillatory activity in the hippocampus. Furthermore, PV and SOM interneurons cooperate to shape the firing of place cells involved in spatial navigation and memory in the hippocampus.

In pathological conditions such as schizophrenia and epilepsy, those functional processes are deeply altered. In animal models related to those diseases, hippocampal rhythms are strongly reduced and recurrently replaced by pathological activity patterns in the case of epilepsy. Neural coding is perturbed, reflected by the disruption of place cells. Those deficits are correlated with behavioral disorders comparable to those observed in patients. Moreover, it has been pointed out that defined subpopulation of inhibitory neurons (and particularly PV and SOM) displayed altered properties. I propose to discuss how I use interneurons as a lever to “equalize” the correct neural coding processes and normalize behavior in animal models of schizophrenia and epilepsy, but also in tissues from patients.


The 2019 CajalXmas

A Christmas meeting at the Cajal

The CajalXmas is an exciting scientific forum at the renowned Instituto Cajal in the heart of Madrid. The long-established meeting brings together young and independent researchers to present and discuss their work in an informal environment before Christmas.

This one-day meeting is conceived to attract neuroscientists with potential interest in joining our institute or independent researchers with interest in scientific collaboration and discussion.

With the collaboration of:

- Biogen
- Fisher Scientific
- Quimigen
- Panlab
Scientific Program

Friday December 20

9.45-10.00  Welcome and presentation

10.00-10.20  Maribel Cuartero  CBMSO, CSIC, Madrid, ES.
10.20-10.40  Francisco José López-Murcia  Max-Planck-Institut, Göttingen, DE.
10.40-11.00  Isabel Espadas  The Scripps Research Institute, Florida, USA.

11.00-11.30  Coffee break

11.30-11.50  Iñigo Ruiz de Azúa  Institut für Physiologische Chemie, Deutsche Resilienz Zentrum, Mainz, DE.
11.50-12.10  Nicolás A. Morgenstern  Champalimaud Foundation, Lisbon, PT.
12.10-12.30  Roberto Leiras González  Department of Neuroscience, University of Copenhagen, DK.

12.40-13.00  Break

13.00-13.20  Antonio Escudero Paniagua  Stein Eye Institute, Los Angeles, USA.
13.40-14.00  Thomas Marissal  INMED, INSERM, Marseille, FR.

14.00-16.30  Poster session & Christmas toast
16.30-18.00  Visits to laboratories and informal discussion

Posters will be placed on display at the Cajal Institute Library (Ground floor) for the whole duration of the meeting.
Differential roles of PI3Ks p110 alpha and p110 beta in synaptic plasticity, neuronal morphology and cognitive function

Class IA phosphatidylinositol-3-kinases (PI3Ks) are heterodimers composed of a p110 catalytic subunit (p110α, p110β and p110δ) and a p85 regulatory subunit1. These PI3Ks synthetize the phosphoinositide PI-(3,4,5)-triophosphate (PIP3), a lipid presents at very low levels in the cell but with key roles in synaptic plasticity, synaptogenesis and cognitive behavior2. While earlier reports suggested that class IA catalytic isoforms could play redundant functions, there is increasing evidence that class IA p110 isoforms are confined to distinct receptor-dependent pathways and importantly, specifically dysregulated in different brain disorders3. However, the differential contribution of each isoform to synaptic plasticity and cognitive processes is still unknown. Here, we used p110α or p110β floxed mice coupled to neuron-specific Cre expression to assess the differential roles of each catalytic isoform in neuronal function. Our results demonstrate that p110α and p110β KO mice display differential phenotypes in both basal transmission and synaptic plasticity paradigms such as long-term potentiation (LTP) and metabotropic glutamate receptor (mGluR)-dependent LTD and suggest a differential requirement of p110α and p110β in the postsynaptic and presynaptic compartment. Furthermore, the absence of p110α or p110β differentially affected spinogenesis and dendritogenesis in hippocampal neurons. Finally, the neuronal-specific deletion of p110α or p110β in the hippocampus caused specific alterations in locomotion, learning/memory and sociability. Thus, our study highlights that p110α and p110β isoforms exert non-redundant functions in neurons, and provides insight into the role of brain PI3K pathway regulating synaptic plasticity and behavior, with potential relevance in the context brain disorders.


Dotti CG, Esteban JA, Ledesma MD. Lipid dynamics at dendritic spines. Front Neuroanat. 2014 Aug 8;8:76.

Complexin enables synaptic strength and prevents premature SV fusion after activity independently on the secondary Ca2+-sensor Synaptotagmin 7

Neurotransmission relies on a precise control of the release of the synaptic vesicles (SVs). Complexin (Cplx) is reported to be the unique protein able to strongly binds SNARE complex, making it essential for neurotransmission. The redundancy of Cplx paralogs expression among synapses albeit at different levels, also hints the relevant function of the protein but complicates the study of its role in synapses in situ by using KO mice. Distinctly to other isoforms, Cpx1-KOs show severe ataxia and tremor, and Cpx1/2 and Cpx1/2/3-KOs die perinatally, indicating that Cpx1 serves synaptic functions partially compensated by Cpx2 and Cpx3. Here, we present for first time how Cplx operates in a high-fidelity central inhibitory synapse by genetically deleting the Cplx1 isoform, the solely paralog expressed in the presynaptic neuron. Cplx-free synapses show a dramatic downregulation of SV release probability that contrast with the overwhelming rates of asynchronous release transiently following activity that were not rescued when monitored it in double-null mice for Cplx1 and the Ca2+sensor reported to be responsible for asynchronous SV release, synaptotagmin 7. Our model postulates that Cplx ensures full-priming of those new SVs that refill the readily releasable pool after synaptic activity, preventing semi-primed intermediate states that trigger premature fusion with the active zone during the elevated residual presynaptic global [Ca2+].
lincRNA D17rik is required in CA1 for the consolidation of Contextual Fear memory

Long-term memory (LTM) storage requires formation of new synapses as well as remodeling of pre-existing synapses. It is known that transcription is essential for these processes during LTM. However, it remains unknown whether and how long noncoding RNAs (lncRNAs) regulate LTM consolidation, due to their complex dynamics of expression. To address this question, we carried out unbiased analyses of gene expression in the hippocampus of mice to identify changes in lncRNAs induced by contextual fear conditioning (CFC). This analysis identified lncRNA D17rik as exclusively expressed in CA1 in fear-conditioned animals compared to controls. To assess the significance of D17rik upregulation in CA1 neurons, we used GapmeRs to knock-down (KD) D17rik and studied its effects in different phases of CFC memory. Our results show that D17rik- KD in CA1 impairs exclusively the consolidation of contextual memory whereas other functions remain intact. This suggests a specific role of D17rik in the underlying process that supports the encoding of contextual fear memory. In addition, localization methods show that D17rik is a cytoplasmic lncRNA and its mechanism of action could be involved in mRNA stability and translational regulation. These results illuminate a novel role for lncRNAs as key regulators of hippocampal-dependent memory consolidation.


A specific prelimbic-nucleus accumbens pathway controls resilience versus vulnerability to develop food addiction

Food addiction is linked to obesity and eating disorders and is characterized by a loss of behavioral control and compulsive food intake. Using a food addiction mouse model, we found that the lack of cannabinoid type-1 receptor in dorsal telencephalic glutamatergic neurons prevents the development of food addiction, which was associated with enhanced synaptic excitatory transmission in the medial prefrontal cortex (mPFC) and in the nucleus accumbens (NAc). In contrast, chemogenetic-induced decrease of neuronal activity in the mPFC-NAc pathway induced compulsive food seeking. Transcriptomic analysis and genetic manipulation identified that increased dopamine D2 receptor expression in the mPFC-NAc pathway promoted the addictive-like phenotype. Our study unravels a new neurobiological mechanism underlying resilience versus vulnerability to develop food addiction.


The striatal microcircuit is composed of medium spiny neurons (MSNs), the principal neuronal type in the striatum, and different populations of GABA- or Acetylcholine (Ach)-releasing interneurons. The activation of these interneurons can broadly modulate MSNs input integration and spiking. Thus, the interaction between local neuronal subtypes impact on striatal output.

The striatum lacks glutamatergic neurons, with most of its excitation arising from the cortex. Two glutamatergic cortical populations project to striatum: intratelencephalic (IT) and pyramidal tract (PT) neurons. These two corticostriatal projections synapse on both striatonigral and striatopallidal MSNs. However, their specific connectivity to striatal interneurons and their polysynaptic effects on MSNs activity, remains unclear.

Using slice electrophysiology, optogenetics and transgenic mice, we found that the activation of PT (but not IT) corticostriatal axons robustly elicits feed-forward excitation in MSNs, through striatal cholinergic interneurons (ChI). Moreover, we described an imbalance in the strength of IT/PT connectivity to MSNs and ChIs in the striatum, supporting the synchronous excitation of ChIs and MSNs by PT, but not by IT. Finally, we found that ChI→MSN signals are mediated by an Ach-dependent glutamate release mechanism involving excitatory long-range axons.

Altogether, these findings expand our understanding of cortex to basal ganglia long-range circuits supporting behavior.
Roberto Leiras González

*Department of Neuroscience, University of Copenhagen, Copenhagen, DK.

Mesencephalic control of locomotion and other motor behaviors: unraveling the Mesencephalic Locomotor Region

The Mesencephalic Locomotor Region (MLR) comprises the pedunculopontine (PPN) and the cuneiform (CnF) nuclei. Previous studies using electrical and pharmacological stimulation shown that both structures are involved in locomotor control. In our research we use optogenetics, electrophysiology, and immunohistochemistry in transgenic mice, to unravel the complex interactions between the sub-structures and distinct cellular populations present in the MLR. We have recently shown (Caggiano & Leiras et al. Nature, 2018) how glutamatergic neurons in the CnF and the PPN modulate gait selection and locomotor speed. Though both nuclei can initiate locomotion, CnF enables high speed locomotor gaits (gallop and bound), while PPN controls slower alternating gaits (walk and trot). Currently, we are studying a PPN glutamatergic subpopulation defined by expression of the transcription factor Chx10. Activation of Chx10+ neurons causes a momentary arrest of all motor behaviors for the duration of the stimulus. The motor arrest not only halts locomotion, but also many other spontaneous motor activities (e.g. grooming and rearing), and modulates essential physiological processes such as respiration and heart rate. These experiments define essential glutamatergic populations for initiating locomotion and controlling locomotor speed, and identify important cellular components of the MLR which control other motor modalities.


Peripherin2 initiates Photoreceptor Outer Segment formation

Photoreceptors are light-sensitive cells of the retina where the visual process begins. These cells contain a modified primary cilium known as the Photoreceptor Outer Segment formation (POS), which concentrates the proteins necessary for light absorption. To do so, the POS is filled with flattened membranes called discs. Discs are continuously being added to the base of the POS and shed from the tip in order to prevent oxidative stress damage. How the POS is renewed has being one of the main questions in the field since it was first described in the 60’s and it is one of the topics we work at in Dr. Williams lab.

Mutations that lead to POS malformation are a common cause of blindness. This way, we know some proteins that are essential for POS formation although we still do not know the specific mechanism by which it is formed. One of these proteins is Peripherin 2. Its loss results in photoreceptors that have a rudimentary primary cilium but it does not contain any discs. In order to study Peripherin 2 role in POS formation we have analyzed Rhodopsin-/-, Peripherin2-/- and double KO mice’s photoreceptors by electron microscopy. This way, we have shown that only cilia expressing Peripherin 2 contain membrane tubules. Also, Peripherin 2 expression in polarized, ciliated cells in culture fills their cilium with membrane. These observations indicates that Peripherin2 is sufficient for the formation of the tubules and suggest that Peripherin 2 is responsible for initiating POS disc formation.


Ernest Palomer Vila

Research Department of Cell & Developmental Biology, University College London, UK.

Rescuing Frizzled 7 in Alzheimer’s Disease, a role for Sirt2

I am interested in understanding how the environment influences brain function in health and disease. In particular, my research focuses on how epigenetic changes favour/impair the transcription of synaptic and memory-related genes.

Suppression of Wnt activity plays a role in Alzheimer’s disease (AD); in particular, the Wnt antagonist Dickkopf-1 is elevated in the AD brain and is required for Amyloid-b (Ab)-mediated synapse loss. However, the role of Wnt receptors remains unexplored in AD. The aim of my research is to analyse in early AD stages the involvement and epigenetic regulation of Frizzled7 (Fzd7), a Wnt receptor involved in synapse formation and plasticity. Preliminary results suggest that FZD7 is downregulated in hippocampal samples of prodromal AD patients. This is consistent with Fzd7 changes in hippocampal samples of the hAPP-NL-G-F AD mouse model at a stage where Ab plaques start to appear. Further, reduced Fzd7 correlates with decreased levels of the active histone mark H4K16Ac and a concomitant recruitment of the histone deacetylase Sirt2 to the Fzd7 promoter. Preliminary results also show that in vitro and in vivo inhibition of Sirt2 in AD models rescues Fzd7 levels, suggesting that targeting Sirt2 in AD could protect against synapse loss and plasticity deficits.


Re-orchestrating the hippocampal neuronal orchestra in mouse models of schizophrenia and epilepsy

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