SAN

SOCIEDAD ARGENTINA DE
INVESTIGACIÓN EN NEUROCIENCIAS

Argentine Society for Research in Neurosciences

Abstracts of the 2019 Meeting of Argentine Society for Research in Neurosciences

XXXIV ANUAL MEETING SAN 2019

VILLA CARLOS PAZ

CÓRDOBA

ARGENTINA

OCTOBER 3-5, 2019

The 2019 meeting of the Argentine Society for research in Neurosciences (SAN) was held at Villa Carlos Paz, Córdoba, Argentina, in Portal del Lago Hotel, from October 3rd to 5th 2019.

There were 350 attendees among researchers, scholars, PhD students and guests from different centers and universities of Argentina and abroad from 8 countries of Latin America, North America and Europe. Our congress had a total of 4 (four) Plenary Lectures, 6 (six) Symposia, 2 (two) Short Conferences, 6 (six) Youth Conferences, 19 (nineteen) Oral Communications, 256 Posters coveringa broad number of areas in the field of neurosciences together with 2 (two) special activities at lunch time and a round table on "Gender and Science".

It is noteworthy that two of the Plenary Lectures were placed in honors of the pioneers of neurochemistry andneurobiology of Argentina, Drs. Ranwel Caputto andEduardo De Robertis. This year the “Ranwel Caputto” Lecture was delivered by Prof. Belen Elgoyhen of the University of Buenos Aires (Argentina) and the “De Robertis” Lecture by Prof. Beatriz L. Caputto of the National University of Córdoba (Argentina). The “Opening Lecture” was given by Prof. Marla B. Feller, Department of Molecular and Cell Biology and Helen Wills Neuroscience Institute, University of California (USA) and the “Hector Maldonado” Lecture by Prof. Lucas Pozzo-Miller Department of Neurobiology, University of Alabama at Birmingham (USA). Short conferences were delivered by Drs. Ethan Buhr of the University of Washington in Seattle (USA), and Emilio Kropff of the Leloir Institute, Buenos Aires (Argentina).

As pre-meeting activity, the specific course for PhD students “Molecular and Cellular Neuroscience and Neurochemistry: Experimental strategies for studying the nervous system in health and disease”, took place on September 30-October 1-2, 2019 at the School of Chemical Sciences of the National University of Córdoba, Córdoba with the participation of more than 60 students.

Remarkably, all the activities organized, including the Symposia and the Young Investigator Lectures, covered a number of diverse disciplines in the field of neurosciences with the participation of outstanding invited speakers from Argentina and other countries.

Moreover, a very friendly atmosphere for discussion and data presentation was generated during the poster and oral communication sessions with the participation of 104 researchers, 139 Ph.D. students, 64 undergrads and 34 postdocs from Argentina**,** Chile**,** Brazil, Uruguay, USA, Canada, Denmark, Germany and France.

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Short Program SAN 2019

Mon., Sept 30th - Wed., Oct 2nd	Thursday, October 3rd		Friday, October 4th	Saturday, October 5th
9:00 - 18:00 PRE-CONGRESS COURSE *"Molecular and Cellular Neuroscience and Neurochemistry: Experimental strategies for studying the nervous system in health and disease"* *Auditorio Ciencias I Facultad de Ciencias Químicas – UNC* **REGISTRATION**	**8:30 - REGISTRATION** **9:00 - 11:00** **SYMPOSIUM I** ***"New perspectives and mechanisms underlying neurological disorders"***		**8:30 - 10:30** **SYMPOSIUM III** ***"Molecular mechanisms of epigenetics and chromatin remodeling during brain development and aging"***	**8:30:00 - 10:30** **SYMPOSIUM VI** ***"Sensory processing and integration in olfactory and tactile systems"***
	11:00 - 11:30 Coffee break		**10:30 - 11:00** Coffee break	**10:30 – 11:00** Coffee break
	11:30 - 12:30 **OPENING LECTURE** Prof. Marla Feller		**11:00 - 13:00** **SYMPOSIUM IV** ***"First impressions: New roles for perinatal factors governing brain development"***	**11:00 - 12:00** **Oral Communications** Room Auditorio (OC 8-12) Room Lago (OC 13-18)
				12:00 - 13:00 **EDUARDO DE ROBERTIS LECTURE** Prof. Beatriz Caputto
	12:30 – Lunch with activities *"The 3Rs in neuroscience research"*		**13:00** - Lunch with activities *"HD Foundation"*	**13:00** – Farewell Lunch
	14:30 - 15:30 **SHORT LECTURES** Ethan Buhr Emilio Kropff	**14:30 – 16:00** **Oral Communications** Room Lago (OC 1-7)	**14:30-15:30** **Young Investigator Lectures** Room Auditorio (YIL 1-3) Room Lago (YIL 4-6)	
	15:30-16:00 **Gender and Science** Verónica de la Fuente			
	16:00 - 17:30 **SYMPOSIUM II** ***"Advances in early diagnosis and in experimental therapy of Alzheimer´s disease"***		**15:30 - 17:30** **SYMPOSIUM V** ***"Sexual differences on development and function of CNS"***	
	17:30 - Coffee break		**17:30** - Coffee break	
	17:30 - 19:30 **Poster Session (Even numbers)**		**17:30 - 19:30** **Poster Session (Odd numbers)**	
	19:30 - 20:30 **RANWEL CAPUTTO LECTURE** Prof. Ana Belén Elgoyhen		**19:30- 20:30** **HÉCTOR MALDONADO PLENARY LECTURE** Prof. Lucas Pozzo-Miller	
	20:30 **WELCOME RECEPTION**		**20:30** **SAN General Assembly**	

ABSTRACTS INDEX

PLENARY LECTURE ABSTRACTS
Thursday 3rd, 11:30-12:30 OPENING LECTURE/Room Auditorio

Wiring up direction-selective circuits in the retina: nature or nurture?
Marla Feller
Paul Licht Distinguished Professor in Biological Sciences Division of Neurobiology, Department of Molecular and Cell Biology & Helen Wills Neuroscience InstituteUniversity of California, Berkeley, USA.

How are circuits wired up during development to perform specific computations? We address this question in the retina, which comprises multiple circuits that encode different features of the visual scene, culminating in over 40 different types of retinal ganglion cells. Direction-selective ganglion cells respond strongly to an image moving in the preferred direction and weakly to an image moving in the opposite, or null, direction. These directional responses are produced by an asymmetry in overall inhibitory conductance onto direction selective ganglion cells, such that object motion in the null direction elicits a greater amount of inhibition from interneurons. I will present recent progress in the lab in characterizing how these properties emerge during development and the role that activity plays in establishing mature circuits.

Thursday 3rd, 19:30-20:30 RANWEL CAPUTTO LECTURE
/Room Auditorio

The Brain Speaks Back to the Ear: The Efferent Olivocochlear System
Ana Belén Elgoyhen
Instituto de Investigaciones en Ingeniería Genética y Biología Molecular, CONICET, Argentina.

In bringing information about the world to an individual, sensory systems perform a series of common functions. Each system responds with some specificity to a stimulus and each one employs some specialized receptor cells at the periphery to translate specific stimuli into electrical signals that all neurons can use. That initial electrical event begins the process by which the central nervous system constructs an orderly representation of for example, sounds, odors, tastes and objects. Thus, basic sound detection begins when sound waves strike the eardrum, which transmits that physical stimulus to the organ of Corti within the cochlea, the sensory epithelium of the mammalian inner ear. Here the primary receptor cells known as inner hair cells transform the information into electrical signals that are sent to the central nervous system by the auditory nerve. However, unlike vision, touch and the chemical senses, sound processing is modulated by efferent signals that travel in reverse, from the brain all the way back to the inner ear, synapsing on outer hair cells. One fundamental question in auditory neuroscience is what role(s) this feedback plays in our ability to hear. During my talk I will present data generated in my lab which has help elucidate the molecular constituents of the efferent-hair cell synapse and the roles of this system.

Friday 4th, 19:30-20:30 HECTOR MALDONADO LECTURE
/Room Auditorio

Ventral hippocampal projections to the medial prefrontal cortex regulate social memory in mice
Lucas Pozzo Miller
Department of Neurobiology, University of Alabama at Birmingham, USA

Inputs from the ventral hippocampus (vHIP) to the medial prefrontal cortex (mPFC) are implicated in several neuropsychiatric disorders. Here, we show that the vHIP-mPFC projection is hyperactive in the Mecp2 knockout mouse model of the autism spectrum disorder Rett syndrome, which has deficits in social memory. Long-term excitation of mPFC-projecting vHIP neurons in wild-type mice impaired social memory, whereas their long-term inhibition in Rett mice rescued social memory deficits. The extent of social memory improvement was negatively correlated with vHIP-evoked responses in mPFC slices, on a mouse-per-mouse basis. Acute manipulations of the vHIP-mPFC projection affected social memory in a region and behavior selective manner, suggesting that proper vHIP-mPFC signaling is necessary to recall social memories. In addition, we identified an altered pattern of vHIP innervation of mPFC neurons, and increased synaptic strength of vHIP inputs onto layer 5 pyramidal neurons as contributing factors of aberrant vHIP-mPFC signaling in Rett mice.

Saturday 5th, 12:00-13:00 EDUARDO DE ROBERTIS LECTURE /Room Auditorio

c-Fos, a dual protein: what we know so far about its lipid activator function in the nervous system

Beatriz Caputto
Departamento de Quimica Biológica-CIQUIBIC CONICET, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina.

c-Fos is a well-established member of the AP-1 transcription factor family whose expression is rapidly induced to transform short-term extracellular stimuli into long-term responses. We established that c-Fos also has another, apparently unrelated, function: it activates lipid biosynthesis. This c-Fos dependent lipid activation has been observed in different cell types: in the chick retina in which light/dark-promoted differences in phospholipid labeling are abolished when c-Fos expression is inhibited; in NIH cells induced to grow and in malignant brain tumor cells in which the same decreasing effect on phospholipid labeling observed upon blocking this activity of c-Fos, inhibits cell proliferation *in culture* and *in vivo*.
Neuronal cell differentiation is crucial for the development and function of the nervous system. This process involves high rates of membrane expansion, where lipid synthesis must be tightly regulated. Blocking c-Fos expression and consequently lipid synthesis activation, impairs differentiation in cells in culture (PC12 cells; hippocampal cells) and *in vivo*, where a strong failure in cortical development is observed in neurons with c-Fos expression blocked or lacking its cytoplasmic activity.
The nature of c-Fos as an intrinsically disordered protein might explain its ability to perform such different functions. The importance of this cytoplasmic activity of c-Fos as a main player in nervous system growth and development will be discussed.

Thursday 3rd, 14:30-15:00 SHORT LECTURES /Room Auditorio

The role of non-canonical opsins on mammalian rhythms in mice

Ethan Buhr
Department of Ophthalmology, University of Washington School of Medicine, Seattle, USA.

Most mammalian tissues express molecular circadian clocks.These clocks exhibit near-24 hour oscillations in transcription and translation. Local circadian clocks must synchronize, or entrain, their rhythms to their surroundings, whether that is the internal body or outside environment. We find the expression of photoreceptive proteins called opsins in many tissues that are naturally exposed to light. In particular, the opsin OPN5 is expressed in the retina, skin, and cornea of mice. The presence of OPN5 is necessary for the correct

circadian phase of these tissues. The direct photo entrainment of circadian clocks in the skin may influence the tissue's response to injury.

Thursday 3rd, 15:00-15:30 SHORT LECTURES /Room Auditorio

Time and space in the GPS of the brain
Emilio Kropff
Fundacion InstitutoLeloir, Buenos Aires, Argentina.

The Hippocampus and the Entorhinal Cortex are key structures for memory and spatial orientation, highly preserved across the evolution of mammals. Hippocampal place cells and entorhinal grid cells are thought to collaborate in our notion of self location, allowing us to navigate daily and reach our destination despite receiving a bombardment of dynamic sensory information along the way. A key operation to achieve this is path integration, or the ability to estimate displacement along short temporal windows based on self motion cues. Theta frequency, a rhythm that modulates the activity of both areas in the rodent brain, has been proposed alternatively as a speed code and as a pacemaker, delimiting each temporal window for path integration. Using the bottom less car paradigm, which allows for the precise control of running speed in rats, we show that the latter hypothesis is more likely to be correct. Our results suggest that the association between theta frequency and speed is derived from a spurious correlation and we propose a model that explains its origins. Variations in theta frequency instead seem to be caused by positive acceleration, perhaps as a way to attenuate systematic path integration errors by using smaller integration windows selectively when those errors are likely to occur.

SYMPOSIUM ABSTRACTS

Thursday 3rd, 9:00-11:00/Room Auditorio
Symposium I

New perspectives and mechanisms underlying neurological disorders
Chairs: Mauricio Galiano, *CIQUIBIC CONICET UNC, Córdoba, Argentina.*
Lionel Muller Igaz, *IFIBIO Houssay, Buenos Aires, Argentina.*

The Integrated Stress Response in Neurodegeneration
María Soledad Matus
Fundación Ciencia & Vida, Santiago, Chile.

Under stress conditions, eukaryotic cells activate a common adaptive pathway, termed theintegrated stress response (ISR), to restore cellular homeostasis. We focus onunderstanding how the ISR can impact brain function in physiological conditions and inneurodegenerative diseases (e.g., amyotrophic lateral sclerosis).

Is Alzheimer´s Disease a Dementia of Neuronal Etiology?
Laura Morelli
Fundación Instituto Leloir, Buenos Aires, Argentina.

Alzheimer is a multifactorial disease, this is why a general pathological mechanism andappropriate treatment have not been found already. Apart from the few individuals with Familial Alzheimer, it is not known why one individual gets Alzheimer late in life and another does not. We are focused on a variety of suspected causes including, genetic background, environmental factors, biochemical disturbances and immune processes.

Role of TDP-43 in neurodegenerative diseases
Lionel Muller Igaz
IFIBIO Houssay, Buenos Aires, Argentina

Neurodegenerative diseases are characterized by progressive dysfunction and loss ofneurons associated with depositions of pathologically altered proteins. The discovery that aggregated transactive response DNA-binding protein 43 kDa (TDP-43) is a majorcomponent of pathological ubiquitinated inclusions in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) caused seminal progress in understanding the etiologyof these now so-called “TDP-43 proteinopathies”. The role of TDP-43 as a neurotoxicity trigger has been well documented in different in vitro and in vivo experimental models. As such, the investigation of TDP-43 pathomechanisms in various major neurodegenerativediseases is on the rise. I will present our efforts to understand the pathophysiological roles of TDP-43, using inducible transgenic mice that recapitulate key features of the ALS/FTD spectrum.

Proteostasis networks in brain health and disease: Protein synthesis control as a main regulator of protein homeostasis
Mauro Costa-Mattioli
Baylor College of Medicine, Houston, Texas-USA

Protein homeostasis (proteostasis) networks are crucially required for normal brain function.
Protein synthesis and its regulation are the primary node of proteostatis control. In thissymposium, I will present our efforts aiming to understand the role of the integrated stress response (ISR), an evolutionarily conserved signaling network that maintains proteostasis by controlling protein synthesis rates in mnemonic processes. A hallmark of many neurological disorders (e.g., Alzheimer’s disease, Parkinson’s disease and aging) is the dysfunction of proteostasis network, hence I will present our new latest findings of how genetic or pharmacological targeting dysregulated translational control pathway that regulate proteostasis may offer therapeutic potential for the treatment of neurological disorders in which the ISR is perturbed.

Thursday 3rd, 16:00-17:30 / Room Auditorio
Symposium II
Advances in Early Diagnosis and in Experimental Therapy of Alzheimer´s Disease
Chair: Diana A. Jerusalinsky, *Lab. Neuroplasticidad y Neurotoxinas, Inst.de Biología Celular y Neurociencia Prof. E. De Robertis, Univ.de Buenos Aires (UBA)-CONICET, Buenos Aires, Argentina*

“Heading to the presymptomatic diagnosis in Alzheimer's Disease” Biomarkers for Alzheimer´s disease: experience in a memory clinic from Latin America
Ricardo F. Allegri
Center for Memory and Aging, Instituto de Investigaciones Neurológicas, FLENI, Buenos Aires, Argentina

Alzheimer's disease (AD) is one of the biggest unresolved health burdens accompanying increased life expectancy. The great paradigm shift for this disease has resulted from finding amyloid deposition 20 years, and

neurobrillary degeneration 10 years prior to onset of typical, clinical memory loss symptoms. Emergence of AD biomarkers has enabled a molecular definition of AD called ATN (Amyloid, Tau, Neurodegeneration), making the clinical definition almost unnecessary. The symptoms mark the localization in the brain but not the etiology. This presentation aimed to describe the role and prognosis of Alzheimer disease biomarkers in patients with mild cognitive impairment at a memory clinic in Latin America. There are different types of AD biomarkers available in our country. Each biomarker reflects a particular process and stage of the disease. Although costs restrict their use, in certain clinical scenarios, biomarker analysis may be justified, such as in cases of early-onset or atypical presentation. Today, no one argues that biomarker application be used in AD clinical research. Incorporation of biomarkers into medical practice however, would also lead to significant changes in therapeutic interventions for patients, even in the context of an absence of disease-modifying drugs.

Familial Alzheimer's disease modeling using a human model of cellular reprogramming

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Alzheimer's disease (AD) is one of the most common neurodegenerative disorders of the elderly, characterized by progressive memory disorientation and cognitive disturbance. The pathological profile of AD is neuronal lossaccompanied by hyper-phosphorylation of Tau and aberrant gamma-secretase activity. Mutations in the genes encoding presenilin-1, presenilin-2 and amyloid precursor protein have classically been identified as the "main *genetic*" causes of*familial AD.*

Adult-onset neurodegenerative diseases are among the most difficult human health conditions to model. To this end, patient-derived induced pluripotent stem cells (iPSCs),generated from easily accessible cells such as dermal fibroblasts or peripheral blood mononuclear cells can be differentiated into neurons,thus providingan unparalleled platform for *in vitro* modelling and development of therapeutic strategies.Moreover, the advent of homology-directed repair techniques for genome editing further expands its benefits.

In this sense, we have successfully reprogrammed fibroblast from a patient suffering from AD and carrying a T119Imutation on presenilin 1. iPSCs were reprogrammed using the Yamanaka factors. Verification of their pluripotency was achieved by demonstrating the expression of pluripotency markers and their differentiation into the three primary germ layers. iPSCs carry the patient T119mutation and present a normal karyotype, hence representing a valuable tool to evaluate the impact of this novel mutation on AD onset.

Are the Abeta Oligomers a Suitable TherapeuticTarget? Sustained Neuronal Expression of an Artificial Antibody selective for ABeta Oligomers protects from Cognitive and Neuronal Alterations

Magali C. Cercato[1]; M. Clara Selles[2]; Alberto Epstein[3]; Anna Salvetti[4]; Adriano Sebollela[5]; Natalia Colettis[1]; Vania F. Prado[6]; Marco A. Prado[6]; Daniela Salas[1]; Martín Habif[1]; Tomás G. Garello[1]; M. Verónica Báez[1]; Fernanda DeFelice[2,7];William L. Klein[8]; Sergio T. Ferreira[2,7,9]*; **Diana A. Jerusalinsky**[1*]

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[6]Dept. of Physiology and Pharmacology and Dept. of Anatomy & Cell Biology, Robarts Research Institute, Molecular Medicine Laboratories, The University of Western Ontario, London, Canada.
[7] Centre for Neuroscience Studies, Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Canada.
[8]Department of Neurobiology, Northwestern University, Evanston, USA.
[9]Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro;and Division of Neurosurgery and Division of Neurology/Epilepsy Program, ClementinoFragaFilho University Hospital, Rio de Janeiro, Brazil.

Alzheimer's disease (AD) is considered the main cause of dementia in aging and despite intense efforts, there is no effective treatment. AD is characterized by amyloid-β peptide (Aβ) accumulation in the brain, leading to soluble Aβ oligomers (AβOs), which have been involved in synaptic dysfunction and memory deficit. Recombinant NUsc1, single-chain variable fragment (scFv) small antibody that specifically targets AβOs, prevented both AβOs-induced inhibition of synaptic plasticity in hippocampal slices and memory impairment in mice with intracerebroventricular (i.c.v.) infusion of AβO. We have developed an adeno-associated viral vector (AAV) to selectively express and secrete NUsc1 from neurons. In culture, AAV-NUsc1 reduced AβO binding to hippocampal neurons and prevented AβO-induced loss of dendritic spines. In vivo, i.c.v. AAV-NUsc1 induces expression and secretion of NUsc1, which recognizes AβOs in wild type mice previously infused (i.c.v.) with hAβOs, in aged APPswe/PS1dE9AD mice and in McGill-R-Thy1-APP rats, improving memory acquisition in the first two. AAV-NUsc1 induces NUsc1 expression in adult human brain cultured slices. Although there are ongoing clinical trials involving gene therapy or antibodies, to the best of our knowledge there are no trials using a vector to drive sustained production of a small antibody targeting AβOs. Our results strongly suggest that AAV-NUsc1 is a potential tool aimed at preventing synapse damage and memory impairment in AD.

Friday 4, 8:30-10:30 h/ Room Auditorio
Symposium III

Molecular mechanisms of epigenetics and chromatin remodelling during brain development and aging
Chair: Alejandro Villareal, *Inst.de Biología Celular y Neurociencia Prof. E. De Robertis, Univ.de Buenos Aires (UBA)-CONICET, Buenos Aires, Argentina.*

Epigenetic Control of Neural Stem Cells During Corticogenesis
Federico Calegari
DFG-Research Center for Regenerative Therapies, Cluster of Excellence, TU-Dresden, Germany

During development, the switch of neural stem cells (NSC) from proliferation todifferentiation establishes the shape and size of the adult brain. To unravel the role ofepigenetic marks in the switch to neurogenesis, we isolated proliferating NSC, neurogenicprogenitors and newborn neurons during mouse cortical development and assessed their DNA (hydroxy-)methylation signatures. Interestingly, cell type-specific differential methylation wasfound enriched in neurogenesis-related genes and bHLH transcription factor binding motifs.We next sought

to site-specifically manipulate DNA methylation to assess the role of epigeneticmarks in programming and reprogramming of NSC by Cas9-mediated delivery of DNAmethyltransferase (DNMT3a) or Tet methylcytosine dioxygenase (Tet1) in developing mouseembryos by in utero electroporation. This approach allowed us to site-specifically manipulate DNA methylation and validate the role of locus-specific epigenetic marks in gene expressionand reprogramming of NSC in vivo.

Transcriptional control of alternative splicing

Alberto R. Kornblihtt

Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE-UBA-CONICET) and Departamento de Fisiología, Biología Molecular y Celular, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina.

Evidence on the co-transcriptionality of splicing and on a role for the transcriptionmachinery on splice site selection produced a radical change in the view of regulatory mechanisms of splicing, originally conceived as a purely post-transcriptional event. Weshowed that alternative splicing (AS) is coupled to RNA polymerase II (RNAPII) transcriptionand envisioned two non-exclusive models: AS is affected by the recruitment of splicing factors to the transcription apparatus (recruitment coupling) or by the speed of RNAPII elongation (kinetic coupling). We demonstrated that transcription by a slow mutant of RNAPII promoted higher exon inclusion, by favoring recruitment of splicing factors to the splice sites in the pre-mRNA. Slow elongation can also promote skipping of certain alternative exons by favoring recruitment of negative splicing factors to their target sites in pre-mRNA. Changes in elongation can be elicited by changes RNAPII CTD phosphorylation and/or by changes in chromatin structure. An example of the first mechanism is the regulation of AS by DNA damage caused by UV irradiation. As for the roles of histone marks and chromatin structure on splicing, a whole fascinating chapter of RNA biology is being written. Specific histone marks, nucleosome positioning, non-coding RNAs affecting chromatin structure and were shown toregulate AS. I'll discuss examples of the physiopathological roles of the transcription/AS coupling and new evidence on how these mechanisms can be used in therapeutic approaches to hereditary disease.

Epigenetic consequences of cholesterol loss in the aging brain

Mauricio Martín

Instituto de Investigaciones Médicas Mercedes y Martín Ferreyra INIMEC-CONICET-Universidad Nacional de Córdoba, Córdoba, Argentina, and Centro de Biología Molecular Severo Ochoa, Universidad Autónoma de Madrid, Madrid, Spain.

Aging is characterized by a progressive decline in cognitive capacities. Severalrecent reports indicate that epigenetic mechanisms are affected in the aged brain andcontribute to the aged brain phenotype. It is, however, unclear whether or not and how typicalfeatures of old brain neurons, i.e. reduced proteasomal activity, impaired mitochondrialfunction, altered lipid composition, participate in the epigenetic regulation of learning-memorygenes. We have analyzed the effect of hippocampal membrane cholesterol loss, a constitutivefeature in aging, on the epigenetic regulation of the Bdnf gene. We found that hippocampalmembrane cholesterol loss induces a repressive chromatin structure in old neurons anddiminishes Bdnf transcription. Oral administration of Voriconazole, an inhibitor of the cholesterol catabolic enzyme cholesterol-24-hydroxylase in mammalian brain, rescued hippocampal age-associated cholesterol loss, Bdnf expression and improved cognitive abilities of old mice. These results unveil one of the mechanisms involved in the cognitive decline ofthe old and propose Cyp46A1 inhibition as valuable therapeutic possibility.

Transcriptional control through histone modifications: radial and longitudinal patterning of the developing cerebral cortex

Tanja Vogel
Institute of Anatomy and Cell Biology, Albert-Ludwigs-University Freiburg, Germany

Precise specification of the different neuronal cell types and their circuit connectionsin the cerebral cortex are fundamental for cognitive functions. Different areas of the cerebral cortex, defined by their diverse functions, are characterised by specific cyto- and chemo-architecture, efferent and afferent circuitries, as well as variable gene expression patterns across the longitudinal and radial axis. The developmental programs that orchestrate proper specification of neuronal networks are genetically determined. Disturbance of these tightly regulated programs cause significant changes in behavior, and are a neurodevelopmental basis of cognitive diseases. A growing body of data shows that histone methylations have important impact on CNS development and function. We will discuss the role of such epigenetic mechanisms on the developing cerebral cortex in general. Specific focus will be laid on the role of histone H3 lysine 79 methylation (H3K79me) which balances transcriptional induction of instructive transcription factors during neurogenesis and thus cortical layering. In this regard, H3K79me might providean epigenetic landscape that can facultatively be used to direct neuronal lineage specification. With regard to longitudinal patterning we will discuss the impact of histone demethylation that help generating gradual activity of transcription factors conferring area identity.

Friday 4, 11:00-13:00 h/ Room Auditorio
Symposium IV

INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION

First impressions: New roles for perinatal factors governing brain development
Chair: Carla Cisterna, *Neuroscience Institute. Georgia State University, Georgia, USA*.

The role of parturition in brain development
Nancy Forger
Neuroscience Institute, Georgia State University, Georgia, USA.

Most mammals enter the world in a fairly dramatic fashion. A vaginal birth is accompanied by marked hormonal changes, mechanical stimuli associated with labor and delivery, and a transitionfrom the sterile environment of the womb to one teeming with microorganisms. The effects of labor and delivery on the fetal/neonatal lungs, circulation, and immune system are well established, yet very little is known about how parturition affects the brain. We recently found that both the mode of birth (vaginal versus Cesarean delivery) and the presence of microbes at birth shape brain development. For example, neuronal cell death is a widespread developmental process that occurs primarily during the first postnatal week in mice. We find an acute inhibition of neuronal cell death following a vaginal delivery that is absent, or reversed, in mice delivered by Cesarean section. The effect of delivery mode on cell death was greatest for the paraventricular nucleus of the hypothalamus (PVN), and was associated with a reduction in the number of PVN vasopressin neurons later in life. To determine whether the neonatal brain is affected by the microbes that are encountered at birth, we compared neuronal cell death and microglial colonization in the brains of mice born conventionally versus those born into a germ-free environment. Neuronal cell death was altered in germ-free mice in a brain region-specific manner and microglial labeling was increased in all brain regions of germ-free newborns; remarkably, both of these changes were seen within the first day of life. The mechanism(s) whereby microbes signal the brain within hours of birth is not known and is currently being investigated. Prior to the advent of Cesarean sections and sterilization, all

eutherian mammals arrived via a vaginal birth into a world filled with bacteria. It is likely that our brains evolved to "expect" these events and that perturbations alter neural development.

Synthetic progestin, neural development, and cognitive behavior: a rodent model investigation of a drug used in human pregnancy

Christine K. Wagner
Department of Psychology, University at Albany State University of New York, New York, USA.

The synthetic progestin, 17α-hydroxyprogesterone caproate (17-OHPC) is administered to pregnant women at risk for preterm birth in the U.S. despite little understanding of the potential effects on the developing brain. Rodent models demonstrate that the mesocortical dopamine pathway is sensitive to progestins during development. Nuclear progesterone receptor (PR) is expressed perinatally in dopaminergic cells of the ventral tegmental area that project to the medial prefrontal cortex (mPFC) and in target neurons of the mPFC during periods of dopaminergic synaptogenesis. Indeed, exposure to 17-OHPC during development increased the density of tyrosine hydroxylase-ir (THir) fibers within the prelimbic mPFC in juveniles and impaired cognitive flexibility in adulthood. 17-OHPC treated rats were slower to learn a shift in reward contingency and made more perseverative errors than controls. In more recent studies, we found a novel sex difference in dopaminergic innervation patterns within the mPFC of the neonatal rat and a differential effect of 17-OHPC in males and females. In a Delay Discounting task, 17-OHPC treated males were more likely to wait for a delayed, larger reward over an immediate, smaller reward than controls and made more omissions, suggesting impairments in decision making and attention. Taken together, these findings highlight the need for a re-evaluation of the benefits and potential outcomes of prophylactic progestin administration during pregnancy.

Cognitive and emotional deficits reflect altered epigenetic mechanisms in hippocampus andamygdala derived from perinatal malnutrition in a mouse model- Reversion with environmentalenrichment

Mariela Chertoff
Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires and IQUIBICEN, CONICET, Argentina.

The quality of the embryonic environment and postnatal experiences have a great influence on the emotional and cognitive development of the infant and the adolescent. We study the impact of perinatal protein malnutrition, using a both sexes young adult mice born from dams fed with normal protein diet (NP) or low protein diet (LP) during pregnancy and lactation. Through a preclinical PET analysis, we found evidence of changes in glucose metabolism in the hippocampus and amygdala of LP mice, suggesting a potential alteration in the function of these areas. Therefore, we performed different behavioral tests in order to evaluate emotional status and memory. We found that recognition memory was impaired and anxiety-like behavior was increased in LP mice. We observed that environmental enrichment (EE) partially reverts the emotional and cognitive deficits. In order to understand the molecular mechanisms behind this, we focus on DNA methylation pathways, finding an increased expression of DNMT3b and Gadd45b in P21 malnourished females but not in males. The5hmC seems to be an important epigenetic mechanism of brain adaptation, so, we examine the distribution of 5hmC on ventral hippocampus and we found several anxiety-related genes differentially 5hmethylated on malnourished mice, which are reverted after growing on EE. Together, these findings represent a critical step toward understanding the molecular effects of the environment on the mechanisms that underlie anxiety disorders.

Developmental changes and sex differences in DNA methylation and demethylation in the postnatal mouse brain

Carla D. Cisternas

Neuroscience Institute, Georgia State University, Georgia, USA.

DNA methylation is dynamically modulated during postnatal brain development in mammals, andplays a key role in neuronal lineage commitment. Many sex differences in the brain are alsoorganized by gonadal testosterone perinatally. To test if DNA methylation is involved in the sexualdifferentiation of neurochemical phenotype (i.e., the number of cells expressing specificneurochemical markers), we first inhibited DNA methylation in the brains of mice during the critical period of sexual differentiation. We found sex-specific effects: the inhibition of DNA methylation increased calbindin-expressing cells only in females, and estrogen receptor alpha cells only in males. As a result, sex differences were reduced or eliminated in the treated groups. DNA methylation depends on a balance between the addition of methyl groups by DNA methyltransferases (DNMTs), and their removal by ten-eleven translocases (TETs). We therefore examined sex differences and developmental changes in these enzymes. We found unusually high levels of DNMTs and TETs in the neonatal brain, with TET activity mirroring gene expression. Sex differences in gene expression were also found in neonates, favoring de-methylation in the male hypothalamus. Neonatal testosterone treatment of females partially masculinized enzyme expression. Thus, sex differences in DNA methylation may primarily be due to differences in de-methylation, which may underlie the sexual differentiation of neurochemical phenotype.

Friday 4, 15:30-17:30 h/ Room Auditorio
Symposium V
Sexual differences on development and function of CNS
Chairs: Mariela Chertoff, *Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad deBuenos Aires and IQUIBICEN, CONICET, Argentina.*
Maria Veronica Baez, *Inst.de Biología Celular y Neurociencia Prof. E. De Robertis, Univ.de Buenos Aires (UBA)-CONICET, Buenos Aires, Argentina.*

Sex related differences in the neuronal control of rest and oviposition in Drosophila melanogaster
Lorena Franco
Centro Atómico Bariloche, Comisión Nacional de Energía Atómica (CNEA), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), San Carlos de Bariloche, Río Negro, Argentina.

Biological clocks allow organisms to anticipate changes in the environment to achieve adequate adaptation. Rest-activity patterns as well as oviposition behaviors are physiological processes that are under the control of the circadian clock. The rest-activity cycle is seen in both males and females of Drosophila melanogaster. However, there are some important sex differences related to the rest timing during daylight hours. It seems likely that this difference can be attributed to different patterns of foraging and especially to a search for egg-laying sites in mated females. In order to characterize these differences and also to identify the neurons that influence rest patterns and egg-laying in mated females we analyzed the locomotor activity and the oviposition behavior. We compared several clock mutant and wild type mated flies under both cyclic and constant environmental conditions. For this purpose, we tracked the fly motor activity in a custom-built arena and also, developed an automated device for monitoring the timing of oviposition in a circadian fashion. In this talk I will summarize some of the results that we have obtained related to the role of different central and peripheral neurons in the control of both locomotor activity and oviposition.

Sex differences in blood pressure regulation and body fluid homeostasis: angiotensinergic and vasopressinergic sexual dimorphisms
Ximena Caeiro
Instituto de Investigación Médica M y M Ferreyra, INIMEC-CONICET-Universidad Nacional de Córdoba. Córdoba, Argentina.

Considerable clinical and experimental data indicate that sex matters when it comes to blood pressure regulation, rates of cardiovascular disease, symptoms and risk factors. Although the awareness of sex differences in cardiovascular disease is increasing, much of what we know about blood pressure regulation has been derived from studies in males. However, principles learned in male models do not necessarily apply to females, and this addresses the importance of studying in more detail the sources of physiological disparity between sexes. Angiotensin and vasopressin differentially modulate hydroelectrolyte and cardiovascular responses in male and female. But are the activational and organizational hormonal effects the only to blame for such differences? Males and females not only differ in their sex (males are born with testes and females with ovaries) but also carry different sex chromosome complement (SCC) and are thus influenced throughout life by different genomes. A growing body of evidence indicates that some sexually dimorphic traits cannot be entirely explained solely as a result of gonadal steroid action but may also be ascribed to differences in SCC. In this symposium, we will discuss our recent studies in which we have demonstrated the contribution of hormonal and sex chromosome complement factors to sex-related differences in angiotensinergic and vasopressinergic involvement in body fluid homeostasis and blood pressure regulation. For this purpose, we used gonadectomized micein which the effect of gonadal sex and SCC is dissociated, enabling comparisons among XX and XY females and XX and XY males. Understanding in more detail the foundational sources of sexually dimorphic traits may offer important insights into designing improved oriented sex-tailored therapeutic treatments in the future.

Sexual differentiation of the brain as a risk factor in the development of autism-related behaviors

Amaicha Mara Depino

Departamento de Fisiología, Biología Molecular y Celular, FCEyN, UBA. Instituto de Fisiología, Biología Molecular y Neurociencias, UBA-CONICET

Autism Spectrum Disorder (ASD) is characterized by poor social interaction and communication, and the presence of restricted interests and repetitive, stereotyped behaviors. Remarkably, four boys are diagnosed with ASD for every girl, showing a striking male bias in prevalence. Using an animal model of ASD, we are studying the biological processes underlying this higher susceptibility in males and/or the higher resilience in females.

Prenatal exposure to valproic acid (VPA) results in adult male mice that interact less with novel social stimuli, exhibit repetitive behaviors and show other behavioral and biological features related with ASD. Interestingly, we found that female offspring prenatally exposed to VPA show normal social behavior, recapitulating what is observed in humans. We then found that exposing females to a second stimulus linked to ASD (postnatal inflammation) results in altered social behavior. These results suggest that female mice are resilient to develop behavioral alterations upon prenatal exposure to VPA.

We will finally present some novel hypotheses on the role of the sexual differentiation of the brain as a risk factor for ASD and data supporting this hypothesis.

Dicer1 is required for pigment cell and craniofacial development in zebrafish

Andrea Weiner

Instituto de Biologia Molecular y Celular de Rosario (IBR-CONICET)- Rosario.

The multidomain RNase III endoribonuclease *DICER* is required for the generation of most functional microRNAs (miRNAs). Loss of *Dicer* affects developmental processes at different levels. Here, we characterized the zebrafish Dicer1 mutant, *dicer1*^{sa9205}, which has a single point mutation induced by N-ethyl-N-nitrosourea mutagenesis. Heterozygous *dicer1*^{sa9205} developed normally, being phenotypically indistinguishable from wild-type siblings. Homozygous *dicer1*^{sa9205} mutants display smaller eyes, abnormal craniofacial development and aberrant pigmentation. Reduced numbers of both iridophores and melanocytes were observed in the head and ventral

trunk of *dicer1*^{sa9205} homozygotes; the effect on melanocytes was stronger and detectable earlier in development. The expression of *microphthalmia-associated transcription factor a* (*mitfa*), the master gene for melanocytes differentiation, was enhanced in *dicer1*-depleted fish. Similarly, the expression of *SRY-box containing gene 10* (*sox10*), required for *mitfa* activation, was higher in mutants than in wild types. *In silico* and *in vivo* analyses of either *sox10* or *mitfa* 3'UTRs revealed conserved potential miRNA binding sites likely involved in the post-transcriptional regulation of both genes. Based on these findings, we propose that *dicer1*participates in the gene regulatory network governing zebrafish melanocyte differentiation by controlling the expression of *mitfa* and *sox10*.

Saturday 5, 8:30-10:30/ Room Auditorio
Symposium VI

ISN
International Society for Neurochemistry

Sensory processing and integration in olfactory and tactile systems
Chairs: Fernando Locatelli, *Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE-UBA-CONICET) and Departamento de Fisiología, Biología Molecular y Celular, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina.*
Matias Goldin, *Unité de Neurosciences, Information et Complexité, Centre National de la Recherche Scientifique, Gif sur Yvette, France.*

Maps and neural codes in whisker somatosensory cortex
Daniel Feldman
Helen Wills Neuroscience Institute and Dept. of Molecular & Cell Biology, University of California Berkeley, Berkeley, USA.

Topographic maps are a canonical feature of sensory cortex, but their precise organization and how they impact sensory coding are often unclear. Maps, sensory coding, and plasticity can be studied efficiently in rodent somatosensory cortex (S1), which contains a prominent map of the facial whiskers. Whiskers are active tactile sensors that extract information about the location, shape, and surface properties of objects. In the classical 'one-whisker-one-column' model of S1, each whisker activates one cortical column in S1, whose neurons act as single-whisker feature detectors. Butcellular-resolution calcium imaging reveals a different, salt-and-pepper organization in L2/3 in which intermixed cells within each column are tuned to different whiskers. Recent studies have shown how this salt-and-pepper map arises in the S1 circuit, how it is structured in awake, behaving animals, and how it is modified by sensory experience.
A major puzzle is how S1 encodes complex spatiotemporal patterns of whisker deflection, which are prominent during natural whisking on objects. We recently discovered that most S1 neurons are sharply tuned within an elementary subspace of 2- whisker sequences that represent local motion vectors on the whisker pad. This tuning is highly organized in the S1 map, with each cortical column representing the set of all local motion vectors involving the columnar whisker. This tuning for local tactile motion is analogous to direction selectivity in vision, revealing a common neural computation across touch and visual systems.

Processing mechanosensory cues during spatial navigation
Hernán Lopez-Schier
Research Unit Sensory Biology & Organogenesis (SBO) Helmholtz Zentrum München Munich, Germany.

For animals that can be displaced by currents, visual signals are the most salient sensory cues to evaluate self-motion relative to an external reference frame. Yet, in the absence of visual information mechanosensory cues can help animals orient in space. Using zebrafish orientation to the direction of water currents, an innate behavior called rheotaxis, we will show how larval zebrafish exploit mechanical inhomogeneities across the horizontal plane to determine water-flow direction. Using a predictive model to guide experimental manipulations, we will show that neuronal directional tuning, as opposed to fine-grained topographic mapping, accounts for rheotaxis. Our data provide a framework for further understanding how images of the mechanosensory scene are formed in the brain and used for spatial orientation. The importance of these results rest on the fact that mechanosensory systems provide an excellent general model to probe the how directional selectivity signals are processed in the brain.

Distinct granule cell population are uniquely engaged in odor learning
Mariana Alonso
Perception and Memory Laboratory, Department of Neuroscience Pasteur Institute Paris, France.

Olfaction is an important sensory modality driving fundamental behaviors. To determine whether an odor is good or bad, the brain essentially needs to attribute a significance to this sensory stimulus. The allocation of a positive significance to an odorant usually depends on its association during learning with a reward outcome. Moreover, multiple forms of plasticity are involved when such odor-reward associations are formed. In the adult olfactory bulb, the continual production of newborn interneurons contributes to the functional plasticity of the system. We demonstrate that adult-born neurons, but not preexisting ones, contain information about learned positive significance. We also found that adult-born neuron activation heightens olfactory learning and enhances the ability to update the odor significance. Moreover, we reveal that adult-born cells are massivelyconnected by higher brain regions and these contacts might be sensitive to odor experiences. In summary, our results show a specific involvement of adult-born neurons in booting odor-reward association that is linked with a distinct connectivity within the olfactory system, and unveil the relevance of encoding odor significance at early stages of sensory processing.

Context and experience dependent representation of olfactory information in the piriform cortex
Antonia Marin-Burgin
Instituto de investigación en Biomedicina de Buenos Aires (IBioBA) CONICET - Max Planck Society Buenos Aires, Argentina.

Olfaction is highly dependent on past experience, present context and the animal's internal state, therefore the olfactory system constitutes an interesting model to study flexible processing of sensory stimuli. The piriform cortex (PC), the largest subregion of the olfactory cortex, receives afferent sensory inputs from the olfactory bulb and top- down inputs from higher-order association areas, such as the amygdala and entorhinal cortex. The nature of these inputs to the PC suggests that its olfactory representations may be modulated by other aspects of sensory experience, like spatial context, hedonic valence and expectation. We study if associative olfactory learning modifies odor- evoked activity in the PC, in a context- and experience-dependent manner. Mice were trained in a Go-NoGo behavioral task to associate an odor with a reward when presented in a specific spatial context. By using silicon probes to record activity of individual neurons in PC, we observed that some neurons showed odor-locked spiking activities that were modulated by context, reward and licking response. In addition, analysis of the population response of neurons using Principal Components Analysis reveals different population dynamics not only dependent on the odor, but also context and reward, suggesting that the PC encodes other attributes that are relevant to the odor experience.

YOUNG INVESTIGATOR LECTURES

Friday 4, 14:30-15:30
YIL 1-3/Room Auditorio
Chair: Mariano Bisbal

YIL 1 _ Parsing a mental program on visual search in natural scenes: Fixation-related brain signatures and models of unitary operations and routines

Juan E.Kamienkowski
Laboratorio de Inteligencia Artificial Aplicada, Instituto de Ciencias de la Computación (FCEyN, UBA - CONICET).

Visual search involves a sequence of unitary operations (i.e. fixations) embedded in a larger mental global routine. The process can indeed be seen as a program based on a while loop (*while the target is not found*), a conditional construct (*whether the target is matched based on specific recognition algorithms*) and a decision making step to determine the position of the next searched location based on the accumulated evidence throughout the trial. Recent developments in our ability to co-register brain potentials (EEG) during free eye movements has allowed investigating brain responses to fixations (fixation-related Potentials; fERPs), including the identification of sensory and cognitive local EEG components linked to individual fixations. However, the way in which the mental program guiding the search unfolds has not yet been investigated. Here, we introduce a data-driven framework to link oscillations and fERPs with the underlying complex mental programs executed in natural viewing. This framework is supported by our previous EEG and eye tracking co-registration experiments, in which participants searched for a target face in natural crowds scenes. In those experiments, we showed how unitary steps of the program are encoded by specific local target detection signatures, and how the positioning of each unitary operation within the global search program can be pinpointed by changes in the EEG signal amplitude as well as the signal power in different frequency bands. By simultaneously studying brain signatures of unitary operations and those occurring along the sequence of fixations, our study sheds light into how local and global properties are combined in implementing visual routines in natural tasks. Finally, new insights drawn from a novel computational model are related to the previous framework. The model combine top-down integration along fixations based on the ideal bayesian searcher model, and bottom-up scene processing based on convolutional neural networks.

YIL 2 _ The histone methyltransferase G9a promotes axonal growth and neuronal development by regulating the RhoA pathway

Carlos Wilson[1,2], Luciana Giono[3], Victoria Rozés-Salvador[1], Alberto Kornblihtt[3], Alfredo Cáceres[1,2]
1 Instituto Ferreyra (INIMEC-CONICET-UNC),
2 Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC), Córdoba,
3 Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE-UBA-CONICET), Buenos Aires, Argentina.

Neurons are polarized cells characterized by the presence of dendrites and the axon, two highly specialized compartments. Several mechanisms controlling polarization have been described, but its genetic regulation has remained understudied. In this regard, epigenetics is a global mechanism for gene regulation, based on modifications of histones and DNA that remodel chromatin conformation. Emerging evidence links epigenetic regulators with neuronal functions in health and disease. Among these, the enzyme G9a, which methylates lysine 9 of histone 3 (a repressor code for gene expression), has been associated with broad aspects of neuronal life, ranging from neurogenesis to chronic pain. Nevertheless, its contribution to early neuronal development is missing. In this work, using both in vitro and in vivo neuronal models, we describe that genetic suppression of G9a inhibits polarity acquisition, axonal growth and cortical migration of developing neurons. Moreover, the loss of function of G9a increased the activity of both RhoA and Rho-dependent kinase (ROCK), two major inhibitors

of axonal growth. Accordingly, mRNA levels of Lfc (a guanine exchange factor of RhoA) were enhanced after G9a inhibition. Together, our data suggest that G9a represses by default the RhoA/ROCK pathway at early stages of development, reporting a novel mechanism controlling neuronal growth and function.

YIL 3 _ Cortical-like dynamics emerge in recurrent neural networks optimized for sampling-based probabilistic inference

Rodrigo Echeveste[1,2], Guillaume Hennequin[1], Máté Lengyel[1,3]
1 Computational and Biological Learning Lab, Dept. of Engineering, University of Cambridge, Cambridge, UK
2 Instituto de Investigación en Señales, Sistemas e Inteligencia Computacional, sinc(i), FICH-UNL/CONICET, Argentina
3 Department of Cognitive Science, Central European University, 7 Oktober 6. utca, Budapest H-1051, Hungary

The dynamics of sensory cortices show a suite of basic, ubiquitous features that have so far escaped a common, principled theoretical account. These include strong, inhibition-dominated transients at stimulus onset [Ray et al., 2010; Haider et al. 2013], gamma oscillations [Ray et al., 2010], and noise variability [Churchland et al. 2010]-- all stimulus-dependent. We present a unifying model in which all these dynamical phenomena emerge as a consequence of the efficient implementation of the same computational function: fast probabilistic inference. For this, we used a novel approach and trained a recurrent E/I neural circuit model of a V1 hypercolumn. The network was required to modulate not only the mean (as conventional) but also the variability of its stationary response distributions in order to match the corresponding input-dependent posterior distributions inferred by an ideal observer. Remarkably, the optimized network exhibited realistic biological properties for which it was not trained directly. It achieved divisive normalization and displayed marked transients at stimulus onset, as well as strong gamma oscillations, both scaling with stimulus contrast. Crucially, these dynamical phenomena did not emerge in two control networks trained to match mean responses: one not explicitly required to modulate variability, and another trained to keep constant Fano factors (as required by other approaches [Ma et al. 2006]). Further analyses of transients and oscillations in the optimized network revealed distinct functional roles for them in speeding up inferences and made predictions that we confirmed in novel analyses of awake monkey V1 recordings from [Ecker et al. 2010]. Our results offer a principled theoretical account of the basic motifs of cortical dynamics and predict further properties of these motifs that can be tested in future experiments.

YIL 4-6 / Room Lago
Chair: Jeremías Corradi

YIL 4 _ Fyn knockdown RNA therapy reduces levodopa induced dyskinesia in the 6-hydroxydopamine mice model of Parkinson's disease

Melina Paula Bordone
FMED UBA, CEFyBO, CONICET, Argentina.

The management of levodopa (L-DOPA) induced dyskinesia (LID) is one of the greatest challenges in Parkinson's disease (PD). Recently, we have proposed Fyn as a novel target to control LID. Fyn is a Src tyrosine kinase that regulates the N-methyl-D-aspartate (NMDA) receptor by phosphorylation of the NR2B subunit in response to dopamine D1 receptor stimulation. The aim of our work was to genetically reduce Fyn expression to alleviate LID in the 6-hydroxydopamine (6-OHDA) mice model of PD, using a micro-RNA against Fyn (miRNA Fyn). To do that, four miRNAFyn sequences under the control of the synapsin promoter were designed, cloned in lentiviral (LV) vectors and tested *in vitro* for silencing efficiency. We induced degeneration of the dopaminergic pathway by injecting 6-OHDA into the medial forebrain bundle, and selected those mice with a remarked deficit of the

contralateral forepaw. Then, we induced dyskinesia before or after LV intra-striatal injections of the selected miRNA Fyn or a non-silencing control sequence. A group of non-injected animals (no LV) was run in parallel. LID were registered every 3 days for 2 weeks. *Postmortem* dopaminergic denervation was carefully determined in the substantia nigra and striatum. We also determined the striatal protein levels of FosB-ΔFosB, a well-accepted marker of LID, and the phosphorylation status of NR2B subunit by western blot. The selected miRNA-Fyn reduced Fyn protein by ~50% in N2a neuronal cell line and by ~40% in a primary culture of cortical cells, and in ~50% of the miRNA Fyn injected-mice it downregulated LID in the pretreatment and postreatment paradigms of dyskinesia. Those mice responders to the miRNA Fyn therapy had a significant reduction in FosB-ΔFosB compared to the non-responders in both experimental paradigms, and had also a significant reduction in pNR2B/NR2B ratio only in the pretreated group. Our results demonstrate that Fyn is a potential target in future biomedical intervention aimed to control LID.

YIL 5 _ Iron deficiency via modulation of DMT1 and its effect on CNS physiology in a *Drosophila melanogaster* model

María Silvina Marcora[1], Mario Rafael Pagani[2], Aime Balanzino[1], Jorge Correale[3] and Juana María Pasquini[1].
1 Departamento de Química Biológica, Facultad de Farmacia y Bioquímica. IQUIFIB- CONICET, UBA, Argentina.
2 Instituto de Fisiología y Biofísica Bernardo Houssay, Grupo de Neurociencia de Sistemas, Facultad de Medicina, UBA, Argentina.
3 Instituto de Investigaciones Neurológicas Dr. Raúl Carrea, FLENI, Buenos Aires, Argentina.

Iron is essential for cell metabolism and plays a fundamental role in the development of the central nervous system (CNS). The neurological signs of iron deficiency in children include decreased cognitive abilities and behavioral problems which have been associated with hypomyelination (Oski and Honig, 1978; Oskiet al., 1983; Lozoff et al., 2006). Studies from our laboratory employing an *in vivo* gestational iron deficiency model showed alterations in oligodendrocyte (OLG) maturation and, astrocyte (AST) and microglia reactivity (Rosato-Siri et al., 2018). The divalent metal transporter 1 (DMT1) participates in the intracellular export of iron from endosomal compartments as part of the transferrin-bound iron uptake, and also mediates non- transferrin-bound iron uptake. Little is known about the role of DMT1 in glial cells. Recently, it has been reported that DMT1-mediated iron transport promotes OLG maturation and myelination (Cheli et al., 2018). In turn, Malvolio (Mvl) is the only member of the DMT1 family present in *Drosophila melanogaster* and has shown capacity to transport iron, as indicated by previous reports of iron deficiency in Mvl mutants (Bettedi et al., 2011). As we have previously demonstrated a relationship between OLG and AST, we decided to explore the relevance of DMT1 in glial cells employing *Drosophila melanogaster* as an *in vivo* model and studying behavioral and cellular parameters in Mvl mutants. Results showed reduced locomotor activity and impaired habituation capacity of Mvl mutants in an open field paradigm. Inmunofluorescense assays of Mvl mutant fly brains showed no signs of apoptosis. Finally, preliminary analysis of Mvl downregulation in glial cells using the UAS/Gal4 binary system showed decreased locomotion, suggesting that Mvl may impact glial physiology. Further analyses on Mvl downregulation in specific glial subtypes will help unveil the role of DMT1 in the development and maintenance of the CNS.

YIL 6 _ Neuronal functionality and vascular integrity alterations in retina of a mouse metabolic syndrome model triggered by long-term fructose intake

Paz, María Constanza[1]; Barcelona, P.[1] Subirada, P.V.[1]; Ridano, M.E.[1]; Chiabrando, G.[1]; Castro, C.[2]; Sánchez, M.C.[1]
[1]*Departamento de Bioquímica Clínica, Facultad de Ciencias Químicas, UNC. CIBICI-CONICET, Córdoba, Argentina.*
[2]*Laboratorio de Biología Vascular, Facultad de Ciencias Médicas, UNCuyo. IMBECU-CONICET, Mendoza, Argentina.*

Type 2 diabetes is consequence of metabolic syndrome (MS), being diabetic retinopathy (DR) a serious complication and cause of blindness in worldwide. We aimed to analyze markers of vascular integrity and neuronal functionality related to early stages of DR in a model of MS.
C57BL/6 (WT) and Apolipoprotein E knockout (ApoEKO) mice fed with normal diet (ND) or 10% w/v fructose diet (FD) in drinking water from 2 months of age were used. Time-dependent kinetic studies were done from 2 to 6 months of diet.
Hypercholesterolemic ApoEKO mice showed an increase in LDL-Chol, and being fed with FD, showed hypertriglyceridemia and decreased HDL-Chol, as well as hyperglycemia, hyperinsulinemia and glucouse intolerance. Scotopic ERG showed decreased *a*, *b* waves and *OPs* in ApoEKO FD *vs* WT DN, which correlated with increased TUNEL positive cells. High vascular permeability in ApoEKO FD was evidenced by leakage of evans blue (e.v.) and extravasation of albumin and α2-macroglobulin. GFAP expression were observed in astrocytes but not in Müller glial cells (MGCs), so there is no reactive gliosis in retinas of ApoEKO FD, which correlates with normal expression of the GS, indicating normal behavior of the MGCs. However, GFAP immunoreactivity decreased in ApoEKO FD retinal flat mounts, which could explain the reduced integrity of BRB. The expression of HIF, VEGF, TNFα and IL6 mRNA, was not modified in ApoEKO FD, reinforcing the changes observed are associated with early stages of DR. Autophagy mechanism was evaluated, observing no changes of LC3 and p62 expression in ApoEKO FD vs increase in WT FD and ApoEKO ND, which could explain higher cell death in ApoEKO FD retinas.
The results showed ApoEKO FD mice present biochemical alterations of MS, with deleterious implications on retinal function and BRB integrity, as well as on intracellular recycling mechanisms. ApoEKO FD mice could be useful for analyze pathogenic mechanisms of RD, as well as a possible platform for therapeutic strategies.

ORAL COMMUNICATIONS

Thursday 3, 14:30 – 16:00
OC 1 – 7 / Cellular and Molecular Neurobiology / Room Lago
Chairs: Alicia Degano and Marcela Brocco

OC 1 _ Early and long-term effects of stress in male dorsal hippocampus: miRNAomics and behavioral relationship

Felipe I. Aguayo [1], Wladimir A. Corrales [1], Gabriela Díaz-Véliz [2] , Juan Pablo Silva [1] , Felipe A. Olave [1] , Luciano Román-Albasini [1] , Jhon A. Cidlowski [3] ,Jenny L. Fiedler [1]
[1] *Laboratory of Neuroplasticity and Neurogenetics, Department of Biochemistry and Molecular Biology, Faculty of Chemical and Pharmaceutical Sciences, Universidad de Chile, Santiago, Chile.*
[2] *Laboratorio Farmacología del Comportamiento, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile.*
[3] *National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Durham, NC, United States.*

Neuroplasticity is a process that allows short to long-term brain remodeling in response to experiences and changing environment. This includes changes in synaptic remodeling and functional modification of neural circuitries. Acute and chronic stimuli (physical or emotional) triggers the activation of the stress system in which the acute stress allows organism to adapt; while chronic stress lead to a maladaptive response. Different animal models of stress show altered hippocampal-dependent behaviors; nonetheless, little is known about the molecular mechanisms involved. Considering that miRNAs play a key role in gene expression regulation, we evaluated the miRNA profile expression in dorsal hippocampus and the object location task in acute (2.5 h of restraint), acute recovery (24 h after stress) and chronic stress (2.5 h of restraint for 14 days). We showed that hierarchical clustering of miRNA expression profile shows a similarity between acute and chronic stress.

Consistently, acute and chronic stressed animals showed a decrease preference to explore an object in a novel position. Interestingly, acute recovery group displayed not only a similar miRNA profile, but also a similar preference for novel location both compared to controls. The enrichment analysis predicts functional relevance of miRNA roles in modulation of signaling pathways related to cell survival, protein metabolism, inflammation, during the transition between acute and chronic stress.

OC 2 _ TNFR1a as a transducer molecule for the inhibitory effect of anti-ganglioside antibodies on axon regeneration

Bárbara Beatriz Báez, Cristian Bacaglio, Ronald Schnaar, Pablo Héctor Horacio Lopez
Instituto de Investigación Médicas Mercedes y Martin Ferreyra – CONICET - UNC.

Guillain Barrè Syndrome (GBS) is an acute autoimmune polyneuropathy where anti-ganglioside antibodies (anti-Gg Abs) are associated with poor clinical recovery. Anti-Gg Abs exert inhibition of axon regeneration via activation of RhoA/ROCK/CRMP-2 signaling pathways, but the identity of their transducer molecule remains obscure. Based on a proteomic study searching ganglioside interacting proteins and the use of an shRNA-based screening, we identified tumor necrosis factor receptor 1A (TNFr1A) as a transducer protein for the inhibitory effect on neurite outgrowth of an anti-Gg mAb targeting GD1a/GT1b. Silencing TNFr1A abolished the inhibitory effect of anti-GD1a mAb but not anti-GT1b specific mAb on Dorsal Root Ganglion neurons (DRGn), showing specificity on the interaction. These results were confirmed using DRGn cultures from TNFr1A-null mice and the use of an in vivo model of axon regeneration by comparing wild type and TNFr1A-null mice. Interestingly, lack of TNFr1A expression in DRGn abolished the ability of anti-GD1a mAb to activate RhoA pathways. We also identified the pertussis toxin-sensitive guanine nucleotide-binding protein G(i) subunit α-2 as part of the signaling cascade triggered by anti-Gg Abs. We developed mutant forms of TNFr1A at the extracellular stalk region to identify the site of interaction.

OC 3 _ Role of actin cytoskeleton dynamics and its modulator Cofilin 1 in fear memory processing

Candela Medina, Verónica de la Fuente, Arturo Romano
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Synaptic efficacy modulation, in tight relationship with synaptic morphological changes, is proposed to underlie long-term memory processing. Such plasticity is known to occur in dendritic spines. These small actin-rich protrusions from dendrites provide a suitable biochemical compartment to locally control and integrate different inputs, due to spatial confinement. Therefore, spine number, morphology and underlying actin polymerization level can modulate synaptic efficacy in many different ways. Actin cytoskeleton has major regulating factors of its depolymerization such as Cofilin 1 (Cfl1), becoming an attractive target to study processes underlying dendritic plasticity. Using a contextual fear conditioning paradigm in mice, we found that pharmacological induction of depolymerization of actin filaments through the inhibition of LIM kinase, which is in turn an inhibitor Cfl1 activity, causes impairment in memory reconsolidation, as well as in memory consolidation. On top of that, Cfl1 activity is inhibited and its mRNA is downregulated in CA1 neuropil after re-exposure to the training context. Moreover, by pharmacological disruption of actin cytoskeleton dynamics, the process of memory extinction can either be facilitated or impaired.

OC 4 **_ Climbing fiber patterning is impaired by angiotensin II type 2 receptor blockage on postnatal cerebellum**

Florencia Martina Soler Garcia [1], Susana I. Sanchez [1], Frank Schweda [2], Lucia Beatriz Fuentes [1]

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The Renin Angiotensin System (RAS) blockers are associated with fetopathy during the third trimester. Ang II AT2 Receptor has been related to a neuronal differentiation during fetal and postnatal development. In cerebellum, AT2R are located only in the Purkinje cells (PC). PCs guide afferent topography to establish the final neuronal circuit. Changes in PC morphology can result in climbing fiber (CF) multi-innervation or mispatterning. We aim to determine the effect of prenatal AT2R blockage on CF connections and PC topology during postnatal development. Wistar rats were implanted mini-osmotic pumps subcutaneously with AT2 antagonist (PD123319) and vehicle during pregnency. Morphological analysis by indirect immunofluorescence was performed on P5, P7 and P15. The results were at P5, PC number was significantly increased ($p<0.001$), non-significant decrease in the arborization length and VGLUT2+ puncta innervating the PC somata. At P7, a delay in PC morphology development, significant increased in VGLUT2+ ($p<0.01$) and decrease in the dendritic tree ($p<0.05$). At P15, VGLUT2+ and PC morphology were normalized. These changes do not compensate the PCL length ($p<0.05$) or the CF territory ($p<0.05$) both significantly increase on treated animals. The results demonstrate changes in PC topology and CF mis-patterning on treated pups. We observed that some parameters were still alter at P15. This study supports the participation of AT2R on cerebellar cortex organization.

OC5 _ hiPSC- and hNPC-derived Extracellular Vesicles: composition and biological activity

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Extracellular vesicles (EV) are nanovesicles (50-200 nm) released to the extracellular microenvironment by most cell types. EV regulate biological processes by transferring lipids, proteins and miRNA cargo between cells during physiological and pathological conditions. Given their ability to transfer bioactive components and their biocompatibility, EV are increasingly being explored as potential therapeutic agents. Stem cell-derived EV promote endogenous regenerative mechanisms and functional recovery in animal models of the central nervous system (CNS). Whether EV secreted by human induced pluripotent stem cells (hiPSC) and human neural precursor cells (hNPC) might have similar therapeutic potential in CNS diseases is still unknown. Moreover, the molecular and cellular mechanisms responsible for their potential regenerative and immunomodulatory effects are unclear. Here, we used a combination of in silico systems biology, biochemical and optical approaches to evaluate compositional and morphological differences between EV secreted by hNPC and hiPSC. These results will help us to shed some light on how stem cell-derived EV might exert their regenerative effects and improve their therapeutic potential in CNS disorders.

OC 6 _ **Arylalkylamine N-acetyltransferase: Nuclear translocation and potential role in response to blue light in retinal neuron cells**

Maximiliano Nicolas Rios, Natalia Andrea Marchese, Mario Eduardo Guido
CIQUIBIC-CONICET, Córdoba, Argentina.

Aryalkylamine N-acetyltransferase (AANAT) is the key regulatory enzyme in melatonin synthesis. AANAT is present in the pineal gland, retina and other regions where is controlled by the molecular clock and light. The AANAT stability is regulated by cAMP increase promoting important changes in its activity. Vertebrate retina is a photosensitive tissue and is known that prolonged exposition to blue light (BL) causes to retinal damage and

circadian clock disruption. In addition AANAT belong to GNAT-5 family together with histones acetyl transferases. Here we investigated the regulation of AANAT and histone 3 acetylation at lysine 27 (H3k27) in primary cultures of chicken embryonic retinal cells exposed to different L conditions. Cultures exhibited BL induction of AANAT as compared with dark controls (D). Interestingly AANAT showed a localization change, from the cytoplasm to nucleus, increasing in BL, and remain elevated in darkness 1 h after BL exposure. Furthermore, high levels of the phosphorylated enzyme were detected after the BL treatment comparated with the D control, in nuclear fractions obtained from primary cultures together with a significant increase in H3k27 levels after BL treatment. Results suggest that AANAT is a BL-induced enzyme in retinal neuron cells, promoting its phosphorylation and nuclear importation, likely playing important roles in nuclear function in response to BL exposure.

OC 7 _ **Protein malnutrition and premature aging: impact on cognitive skills and cellular senescence**

Nadina M. Ferroni, Eduardo T. Cánepa, Silvina V. Sonzogni
Laboratorio de Neuroepigenética, Departamento de Química Biológica, Universidad de Buenos Aires, and CONICET, Ciudad de Buenos Aires, Argentina.

Early-life adversity, like protein malnutrition, increases the vulnerability to develop long-term effects on brain structures and function. The aim of this work is to study if perinatal protein malnutrition (PM) predisposes the occurrence of premature aging in a murine model and the mechanisms involved. Mice dams were fed with normal (NP, casein 20%) or low protein diet (LP, casein 8%) during gestation and lactation. Female offpring were evaluated at the ages of 2, 7 and 12 month. LP mice show a lower increase of weight along life and a tendency in having a lower mobility test at old age. We evaluated spatial memory and found that PM impairs this memory since they are young. Also, functionality of the olfactory system is lost earlier life in LP mice. We found a higher SA b-gal activity at old age in LP mice in the hippocampus that coincide with a premature upregulation of p21 senescence marker. We also found alterations in hippocampal neurogenesis at an old age showing LP mice a more immature dentate gyrus. Moreover, we evaluated oxidative stress and found a higher basal level in LP hippocampus together with a downregulation tendency of Catalase expression at a young age. We also found an upregulation by PM and age of Sirt7 which is recruited to DNA double-strand breaks. Together, our results show that perinatal PM causes long-term impairment in cognitive and physical skills through an accelerated senescence phenotype and increased in the oxidative stress in the hippocampus.

Sat 5, 11:00 – 12:00
OC 8 – 12 / .Cellular and Molecular Neurobiology /Room Auditorio
.Neurochemistry and Neuropharmacology
Chairs: Marta Antonelli and Gastón Calfa

OC 8 _ **Adipose-derived mesenchymal stem cells and magnetic nanoparticles: different tools combined to promote sciatic nerve regeneration after injury**

Paula Andrea Soto [1], Gonzalo Piñero [1], Vanina Usach [1] ,Marcela B. Fernández van Raap [2], Patricia Setton-Avruj [1]
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Neuropathies constitute a major issue in public health with high prevalence worldwide. Patients' poor clinical evolution turns these affections into a crippling disease, which is why the development of new regenerative therapies is of great importance. Wallerian degeneration is an efficient animal experimental model in mimicking the impact of peripheral nerve lesion to shed light on possible regeneration strategies.

In this context, the aim of the present work was to test whether magneto targeting, a nanotechnological strategy to mobilize magnetic nanoparticles (MNP), can help adipose-derived mesenchymal stem cell-loaded MNP (AdMSC-MNP) reach specific tissue guided by an external magnetic field and thus improve the regenerative ability of AdMSC upon sciatic nerve lesion. To test our hypothesis, AdMSC were extensively characterized, and MNP internalization by AdMSC as well as AdMSC-MNP arrival at the injured nerve were evaluated through microscopy and magnetometry. Finally, cell transplantation effects on regeneration were evaluated both in terms of nerve morphology and conduction. Our results show that AdMSC can internalize 2 to 4 pg MNP/cell and that AdMSC-MNP magneto targeting enhances cell arrival exclusively at the lesion site and their beneficial effects on sciatic nerve regeneration. In short, our results prove that magneto targeting of AdMSC-MNP constitutes a novel and valuable tool to promote nerve regeneration by enhancing AdMSC arrival at the lesion site.

OC9 _ Identification of calcium binding sites and structural determinants that regulate potentiation of α9α10 nicotinic cholinergic receptors

Sofia Gallino [1], Paola Plazas [2] , Juan Boffi [1] , Ana Belén Elgoyhen [1]
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Nicotinic cholinergic receptors (nAChR) are pentameric cation-permeable ion channels activated by acetylcholine (ACh). Each nAChR subunit comprises a large extracellular amino-terminal domain, four transmembrane domains (TM1-TM4) and a long cytoplasmic loop between TM3 and TM4. The α9α10 nAChR mediates the inhibitory synapse between efferent fibers and outer hair cells of the cochlea. Expression of rat α9 and α10 nAChR subunits in Xenopus laevis oocytes yields functional α9 and α9α10 receptors, but not α10 homomeric nAChRs. One of the functional differences between α9 and α9α10 nAChRs is the modulation of their ACh-evoked responses by extracellular calcium (Ca2+). While α9 nAChRs responses are blocked by Ca2+, ACh-evoked currents through α9α10n AChRs are potentiated by Ca2+ in the micromolar range and blocked at millimolar concentrations. In order to identify the structural determinants responsible for these differences, we generated chimeric and mutant subunits, expressed them in Xenopus oocytes and performed electrophysiological recordings under two electrode voltage clamp. Our results suggest that the TM2-TM3 loop of the α10 subunit contains structural determinants responsible for the potentiation of the α9α10 nAChR by extracellular Ca2+. Moreover we identified α10 E45 and E175 as key residues of two potential Ca2+ binding sites involved in this potentiation.

OC 10 _ SARA involvement in modulating TGFβ signaling during neural development

Victoria Rozés-Salvador [1,2], Carlos Wilson [3], Christian Gonzalez-Billault [4], Cecilia Conde[1]
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[2] *Instituto Ciencias Básicas y Aplicadas, UNVM.*
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Several events are necessary for proper neuronal development, such as cytoskeleton dynamics and endosome trafficking. SARA is a protein that binds to early endosomes; performing both traffic and signaling functions, as in the transforming growth factor β (TGFβ) pathway. In this sense, it has been described that SARA recruits Smad2/3, favoring the activation of this pathway; but it can also modulate the inactivation of TβRI by PP1c in both epithelial cells and cell lines. In addition, TGFβ signaling has been shown to specify the axon during neuronal development; however, the participation of SARA in this signaling pathway during development remains unknown. For this reason, we proposed to analyze the role of SARA in TGFβ signaling during neuronal development. Results obtained in cultures of hippocampal neurons, by FRET showed physical interaction

between SARA and TβRI. In addition, performing experiments of loss and gain of function, we found that dominant-negative form of SARA (SARA-F728A) generates greater axonal growth and loss of axonal specification compared to control condition. Interestingly, this mutant alters its binding to the PP1c protein, keeping the TGFβ pathway over-activated. Also by FRET, we find that SARA-F728A has more interaction with PP1c and GADD34 than control, suggesting that SARA prevents TβRI dephosphorylation. These results suggest that SARA negatively modulates the TGFβ pathway, which seems to be a necessary requirement for proper axon specification.

OC _ **11 Serotonin (5-HT) and catecholamines (CA) coordinates antagonistic food-related behaviors in C. elegans**

María Gabriela Blanco [1], María José De Rosa [1], Diego Rayes [1]
[1] *Instituto de Investigaciones Bioquímicas de Bahía Blanca.*
[2] *Departamento de Biología, Bioquímica y Farmacia. Universidad Nacional del Sur*

Despite the intermodulation between serotonergic and adrenergic signals is crucial throughout the animal kingdom, the molecular and cellular mechanisms underlying this interrelation are poorly understood. We here use C. elegans as a model to get insights into the neural circuits linking 5-TH and CA. When food-deprived worms encounter food, 5-HT is released to slow-down their locomotion and to stimulate pharyngeal pumping. In contrast, exogenous Tyramine (TA) and Octopamine (OA), invertebrate counterparts for adrenaline and noradrenaline, stimulate locomotion and decreases pharyngeal pumping. We found that tdc-1 mutants (unable to synthesize TA and OA) are hypersensitive to 5-HT-mediated paralysis, suggesting that TA and OA acts antagonistically to 5-HT. We also identify the TA (TYRA-3) and OA (SER-3 and SER-6) receptors involved in this antagonism. Moreover, our calcium imaging recordings showed that the peak of activity of serotoninergic neurons upon encountering food is significantly higher in tdc-1 null mutant background. Taken together these results suggest that TA and OA counteract serotoninergic signaling by driving opposing behaviors and by inhibiting 5-HT release. Our final aim is to decipher the neural circuit and the molecules involved in the reciprocal modulation between CA and 5-HT in C. elegans. Given the conservation in molecular components of these pathways, our studies are likely significant to understand this interrelation in other animals.

OC 12 _ Behavioral and molecular modulation of the stressed glutamatergic synapse by fasudil, a Rho-kinase inhibitor with antidepressant potential

Luciano Román-Albasini [1], Gabriela Díaz-Véliz [2], Felipe Antonio Olave [1], Felipe Ignacio Aguayo [1], Wladimir Antonio Corrales [1], Juan Pablo Silva [1], Jenny Lucy Fiedler [1]
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Chronic stress modulates brain glutamatergic systems, namely the hippocampus, that may result in depressive and anxiety disorders. Antidepressants trigger molecular and morphological changes at the glutamatergic synapse, including variations in the levels of AMPA and NMDA receptors, resulting in improved plasticity and behavioral outcomes. Considering that Rho-kinase inhibition by fasudil has antidepressant-like actions in rodents, we evaluated whether fasudil elicits changes in AMPA and NMDA subunits levels in hippocampal synaptic fraction of stressed rats and if it prevents stress-induced behavioral impairments. Adult male Sprague-Dawley rats were treated with fasudil (ip., 10 mg/kg/day) or vehicle for 18 days and some animals were daily restrained (2.5 hr/day from day 4 to 18). 24-hr after treatments, elevated plus maze, object location task and western blotting of hippocampal synaptoneurosomes were performed. We found that fasudil prevented stress-induced anxiety-like behavior and loss of novelty preference as indicated by open arms spent time and discrimination index values, respectively. Furthermore, we observed that fasudil reduced synaptic GluA1 and

NR2B levels in stressed animals, while it increased synaptic GluA1 and GluA2 levels in unstressed animals. Our results support the notion that fasudil triggers molecular modulations of the glutamatergic synapse under a stress paradigm preventing behavioral impairments, thus supporting its antidepressant potential.

OC 13 – 18 / .Chronobiology / Room Lago
.Cognition, Behavior and Memory
.Computational Neuroscience
.Sensory Systems
Chairs: María Ana Contin and Juan E. Ferrario

OC 13 _ Glial contribution to circadian structural plasticity in pacemaker neurons of Drosophila melanogaster
Juan Ignacio Ispizua, Maria Fernanda Ceriani
Laboratorio de Genética del Comportamiento. Fundación Instituto Leloir. IIB-BA CONICET. Buenos Aires, Argentina.

Circadian clocks are present in almost all organisms, as they provide a way to adjust their physiology to the daily environmental changes triggered by the rotation of the planet. In the brain of D. melanogaster, this clock comprises 150 neurons that are divided in several clusters according to their anatomical location. Among these groups, the small ventral lateral neurons (sLNvs) are considered the "main pacemaker", as they govern circadian activity patterns in constant darkness. The sLNvs dorsal projections contact specific neuronal clusters differentially across the day. These terminals cyclically change their structure, displaying a highly arborized and desfasciculated architecture in the morning, to a less branched structure in the early night and to an even more retracted form before dawn. These changes modify the way the pacemaker circuitry is wired, but its effects on animal behavior and the molecular basis that control this process are only recently begun to be explored. A few years ago our laboratory described that a functional glial clock is necessary for the coordination of this phenomenon. In this work, we describe in depth this neuronal-glial interaction as a function of the time of day and found that these termini contact directly with two different glial subtypes (astrocyte like and ensheathing glia) and that the contacts with the ensheathing glia are time-of-the-day dependent, suggesting that this subtype actively contributes to the remodeling process.

OC 14 _ Effects of acute and chronic physical activity on Spatial Pattern Separation in humans
Daniela Ramirez Butavand [1], Maria Florencia Rodriguez [3], María Virginia Cifuentes [3], Marcos Lazo [4], Cristian García Bauza [4], Pedro Bekinschtein [2], Fabricio Ballarini [1]
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[3] *CIC, PLADEMA, Universidad Nacional del Centro, Tandil.*
[4] *CONICET, PLADEMA, Universidad Nacional del Centro, Tandil.*

The computational process for differentiating similar input patterns has been referred to as pattern separation. It has been reported that BDNF expression in the dentate gyrus is required for memory consolidation of similar, but not dissimilar, spatial representations. Also, several studies showed that exercise can regulate adult hippocampal neurogenesis, which is known to benefit Spatial Pattern Separation in rodents. For these reasons, in this work, we developed a task in an immersive Virtual Reality environment to assess spatial pattern separation and the effect of exercise on this phenomenon. The task consisted on testing the long-term memory with a variable pattern separation load. This was achieved using similar and dissimilar conditions, where the

position of two flags was separated by 20° and 40°, respectively. First, we evaluated the effect of acute physical activity (Acute) on the consolidation of similar and dissimilar conditions and test them 24 hours later. Also, we studied the phenomenon in a population of athletes (Chronic). Our results showed a significant improvement in memory in the Acute group only in the similar condition compared to the Control group (video of someone exercising). In addition, we observed a trend towards a better performance in the Chronic group, but the difference was not significant. The translational implication of this paradigm could certainly impact on the knowledge of the biological bases of human cognition and mental health.

OC 15 _ Molecular mechanisms in the DG and CA3 regulate the balance between differentiation and generalization during retrieval in a cue-degraded context

Magdalena Miranda, Facundo Morici, Dinka Piromalli Girado, Carla Navas, Francisco Gallo, Noelia Weisstaub, Pedro Bekinschtein

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Because our environment is permanently evolving, it is crucial for episodic memory to remember our previous experiences despite environmental changes. Computational models have suggested the existence of a pattern completion process by which networks could retrieve entire memories from partial or degraded cues. The CA3 region of the hippocampus was proposed to mediate this computation by the plastic enhancement of the recurrent collateral connections of CA3 neurons that were active during learning. In this work, we manipulated the amount of cues available during retrieval (test phase) in a spontaneous object recognition task to investigate the function of CA3 NMDA-receptors (NMDAR) for pattern completion. We show that pharmacological intervention of hippocampal CA3 NMDAR receptors impairs retrieval of the object location memory only when cues are degraded, while similar manipulations in the dentate gyrus have no effect. Moreover, while the context alone is enough o guide retrieval of the object memory under partial cues, antagonists of NMDAR in the test phase prevent this retrieval. These findings suggest that NMDAR in CA3 are necessary for the retrieval of spatial memories when the amount of environmental information is reduced, and that plastic changes in the dentate gyrus and CA3 are important to define if behavioral pattern separation or pattern completion occurs when exposed to a modified context.

OC 16 _ Dynamics of GABABR signaling: influence of cholesterol and aging

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GABA B receptors (GABABRs) are obligatory heterodimers which belong to the superfamily of G protein-coupled receptors (GPCRs). Age-related changes in membrane cholesterol levels modulate membrane fluidity, which in-turn influences GPCRs´ localization and function. We studied the GABABR and also a transmembrane transporter structurally homologous to KCC2. To characterize transient conformational changes over time, molecular dynamics simulations were performed using a neuronal plasma membrane (PM) model. Two different membrane cholesterol levels were evaluated: 45% and 10%, which intend to resemble the composition of adult and aged neuronal PMs, respectively. For experimental verification in both young and aged cerebella, we determined protein expression and distribution, and we assessed whether the two proteins interact with each other in vivo. Techniques were: western blots (WB), co-immunoprecipitation assays, and multiple

immunolabeling followed by confocal microscopy. Our results suggest that the expression and spatial distribution of both proteins change as the cerebellum grows older. Based on our in silico analyses, we infer that a G protein-independent interaction does occur. Also, we confirmed that the two proteins are part of the same complex in the cerebellum. As our simulations indicate, we propose that the underlying mechanism implies transient conformational changes, which are highly dependent on cholesterol levels and are therefore affected by the aging process.

OC 17 _ **Melatonin protects the retinal pigmentary epithelium and photoreceptor damage within experimental non-exudative age-related macular denegeration**

Hernán Dieguez [1], Horacio E. Romeo [2], Agustina Alaimo [3], Maria Florencia Gonzalez Fleitas [1], Ruth E. Rosenstein[1], Damian Dorfman [1]

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[3] *Laboratorio de Dinámica Celular y Nanoherramientas, IQUIBICEN/CONICET/UBA.*

Non-exudative age-related macular degeneration (NE-AMD), the main cause of blindness in the elderly, is characterized by retinal pigment epithelium (RPE) and photoreceptors (PR) atrophy exclusively circumscribed to the macula. There are no effective therapeutic strategies that can prevent or delay the NE-AMD. It has been suggested that RPE oxidative damage plays an important role in NE-AMD pathogenesis. Melatonin is an effective antioxidant and has proven effects within several retinal neurodegenerative disorders. We have developed a NE-AMD model induced by superior cervical ganglionectomy (SCGx) in adult C57BL/6J mice, which reproduces NE-AMD hallmarks exclusively circumscribed to the central temporal RPE/outer retina, a region comparable to the human macula. In this context, the aim of this work was analyzing the effect of melatonin on the alterations induced by SCGx. Melatonin prevented the visual function, the decrease in RPE melanin content and RPE65-inmunorreactivity, and the RPE and PR ultrastructural alterations at 10 weeks post-SCGx. Moreover, melatonin prevented the decrease in mitochondrial mass (MitoTrackerRed (+) area, and levels of specific mitochondrial proteins) as well as the increase in RPE and PR oxidative stress markers at 6 weeks post-SCGx. These findings suggest that melatonin could be a possible novel therapy for treat the dAMD.

OC 18 _ Noise exposure triggers changes in synaptic function in mammalian hair cells

Luis Ezequiel Boero [1], María Eugenia Gómez-Casati [2], Mark Rutherford [3], Juan Goutman [1]

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Noise-induced hearing loss has gained relevance as one of the most important sources of hearing loss. It has been shown that acoustic trauma (AT) producing only transient auditory threshold shifts also produces long-term reductions in the number of synapses between inner hair cells (IHCs) and afferent neurons. Here we intend to address if the capacity of IHCs to release neurotransmitter is altered after AT. Mice were exposed to loud sounds for 1 hour, and evaluated one day later for cochlear function. Exocytosis in IHC was tested by measuring changes in membrane capacitance (ΔCm) triggered by step depolarizations. IHCs from exposed WT mice displayed larger ΔCm jumps compared to unexposed IHCs using short pulses at different voltages. Larger differences were found at the maximal release points in the curve. Also, exposed IHCs showed augmented ΔCm with pulses of extended duration, longer than 100 ms. No differences in calcium entry between exposed and control cells were observed for any of the applied depolarizations. To determine if this potentiated release was

triggered by glutamate released during AT and acting retrogradely, we made use of the vesicular transporter vGluT3 knock-out (KO) mouse. Exposed KO showed reduced ΔCm compared to controls, in contrast to what was observed in WT mice. These results suggest that AT enhances vesicle release in IHC, possibly by accelerating vesicle recruitment, and this would be dependent upon the intense glutamate release.

POSTER ABSTRACTS
Brain Awareness Week Activities

P1.-BAW2019: Do children and worms look alike?
Eliana M. Fernández, Marcela A. Brocco
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Direct experiences forge scientific vocations. Hence, during BAW2019, we visited two elementary schools located in Villa Ballester, San Martín. Our goal was that children of 5th and 6th grade carried out experiments as if they were scientists. To this, we choose to test how the nervous system detects, decodes and responds to environmental cues. Thus we used the worm C. elegans as a model. The worm has a simple nervous system that allows it to detect environmental signals such as predators, food or mates. Perception of these signals permits worm to react properly and guarantee survival. The activity included a comment about nervous system, sensory perception, C. elegans and how it is currently used in various investigations. Next, the scientific method was briefly explained. Then, children tested the hypothesis of weather children and worms look alike. We designed activities with simple sensory experiences for children that were compared with C. elegans behaviors when exposed to different sensory stimuli. Activity was completed with gifts for the participants. Children, teachers and school principals surprised and engaged with activities. All participants enjoyed the opportunity to learn about neurosciences and thanked the link created between school and university.
SAN (BAW) supported the activity.

Brain Awareness Week Activities

P2.-Can you listen? Can you hear me? A talk about audition
Luis E. Boero, Marcelo J. Moglie, Sofia L. Gallino, Agustín E. Carpaneto Freixas, Tais Castagnola, Mariano N. Di Guilmi
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Presenting author: ***Agustin Eduardo Carpaneto Freixas,*** *agustincarpaneto@gmail.com*

Acoustic trauma has become a worldwide problem affecting thousands of people on a daily basis. Generating awareness about this situation is necessary to prevent hearing loss, especially among the young population. In this context, we decided to reach out to primary and middle-school students, not only because they are at a higher risk of harmful noise exposure but also because they can still change their habits into a healthier lifestyle. The project consisted on visiting two schools (Instituto Ramón L. Falcón and Colegio Nacional Buenos Aires) and a music conservatory (Coro Nacional de Niños) and giving a brief interactive talk (20-40 minutes approximately). We decided it was best to start by explaining the basis of the auditory sensory system; namely how sound stimuli are processed at a periferic level and then communicated to the central nervous system. In addition, we tried to demonstrate how harmful some everyday noises might be and the potential risks that being exposed to

them brings. We believe that with a clear understanding of the basis of hearing it is possible to understand the importance of taking care of such a vital sensory system and encourage the population to avoid exposure to high sounds and protect themselves.

Brain Awareness Week Activities

P3.-Musical learning

Joana Asensio[1], Andrea Barauna[1], Martín Chrabalowski[2], Cristina Croce[1], Estefanía Farias Altamirano[1], Leandro Freites[1], Paula López[1], Esperanza Mata Martínez[1], Andrea Páez[2], Elena Vásquez[1]

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Music plays an essential role in human interactions. The harmonic flow of sounds influences directly different brain areas involved in cognitive processes and emotions. Our enthusiastic group organized and offered a dynamic workshop for children between 9 and 10 years old to introduce them to the fascinating world of Neurosciences. We visited 5th grade students in different schools in the city of Mendoza, Argentina. Children were acquainted with basic concepts of the nervous system, neurons and the hearing system. We exposed the connection between sound stimuli and how our brain is capable of interpreting them in order to generate a response accordingly. Students learned how music can help us evoke memories and even affect our mood. Finally, children observed neurons under the microscope and were able to identify different brain areas in whole fixed cow brains. For this purpose, the functional parts of a microscope and basic biosafety precautions were appointed to them. In conclusion, our workshop helped 5th graders come into contact with the exciting world of the brain, making the learning process enjoyable through games and exercises. Our approach proves that music can be an important teaching tool for children, facilitating not only their creativity, but also the uptake and fixation of difficult concepts.

Brain Awareness Week Activities

P4.-The Relator Brain- Short Stories contest about Neuroscience and Life

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Brain Awareness Week (BAW) is the global campaign to increase public awareness of the progress and benefits of brain research in a weeklong celebration every March. This year, with the financial support of the Sociedad Argentina de Investigación en Neurociencias, we organized and coordinated a Contest of short stories related to the area of neurosciences. The activity was open to the whole community from Argentina, Latin America, and Spain. To participate people had to submit a story (300 words maximum) related to neuroscience and its relation with ordinary life. Dr. Diego Golombek, Senior Investigator National Research Council and the writer Milena Giudice, evaluated 28 stories from the category over 18 years and 4 from category between 10-18 years, choosing a first and second place for each one. The stories could be read on Facebook and the general audience

could choose their favorite. We consider the contest successful due to the great number of participants. It was an excellent opportunity to promote and let people know about neuroscience.

Brain Awareness Week Activities

P5.-The cinephile Brain- Short films, talks and debate sessions on neuropathologies

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Brain Awareness Week (BAW) is the global campaign to increase public awareness of the progress and benefits of brain research in a week-long celebration of the brain every March. This year, with the financial support of the Sociedad Argentina de Investigación en Neurociencias, we coordinated a film festival and discussion forum of neuropathologies named "The cinephile Brain". The event was carried out at the National Academy of Science's facilities. Each day was focused on a single pathology: Parkinson's disease, Alzheimer's disease, Autism Spectrum Disorders, Multiple and Amyotrophic Lateral Sclerosis, and Schizophrenia. The activity schedule consisted of an introductory section performed by a young scientist, where they explained the cellular and molecular basis of the pathologies and the experimental approach used in their own research projects. Afterwards, there was a film section where short films, mainly from independent artists, were broadcasted. Finally, there was an open discussion forum with a multidisciplinary panel conformed by young researchers, professionals from the clinic area, patients and/or their relatives. We obtained positive results with a great number of attendants, including a wide age range, and an active interplay between the general audience, researchers, clinic's professionals, patients and their relatives. It was an excellent opportunity to aware about the importance of the scientific contributions in a better understanding of the diseases.

Brain Awareness Week Activities

P6.-BAW 209 – FCEFyN, UNC

Franco Mir, M. Angélica Rivarola, Laura Vivas

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The event, organized by the Cátedra de Fisiología Animal (FCEFyN-UNC), included talks aimed at all audiences, given by professors / researchers of our lab. Curiosities about the brain and its functioning as well as the latest results of our research lines were shared. The event also included a function of the scientific play "El placer de ser hormiga" (The pleasure of being an ant) performed by Tacurú theater group. The play is about how our brain processes love, pleasure and the use of psychoactive substances from a neuroscientific perspective. Both activities were totally free and around 200 assitants enyoed it. The main objective was to create spaces within the University to strengthen ties with the community through curiosity and knowledge

Brain Awareness Week Activities

P7.-BAW 2019 - Bariloche

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"Brain Awareness Week" is a global campaign that aims to increase public awareness of the progress and benefits of brain research. Since 2014, and simultaneously with activities taking place in other centres around the world, we carry on a series of events (talks and exhibitions) in San Carlos de Bariloche. This year we organized 5 talks along the week, free and open to the general public, and we invited experts in different neuroscience topics. The topics of this year's talks were: motor control, memory and sleep, poverty and cognitive development, neurobiological aspects of depressive and anxiety disorders, and animal models of neuropsichiatric diseases. Moreover, we carried out an interactive exhibition, with posters and hands-on experiments, intended for the general public, with particular emphasis on high school students. The impact of these activities in the local community was remarkable. Each talk attracted around 300 assistants, and more than 1200 students visited the interactive exhibition, apart from other visitors. This event was supported by Sociedad Argentina de Investigación en Neurociencias, together with Instituto Balseiro, Cooperativa Eléctrica de Bariloche and other local institutions, and counted with wide press and media broadcasting.

Brain Awareness Week Activities

P8.-Let´s take care about our brain

María Florencia Rossetti, Guillermina Canesini, Rocio Schumacher, Nicólas Fabre, Jorge Guillermo Ramos

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In order to raise awareness among primary school children about the importance of taking care of our brain through 3 fundamental pillars (healthy food, physical exercise and cognitive activity), we visited elementary schools in the province of Santa Fe and developed the following activities: (1) We explained through a small puppet play and a song how different environments affect the brain´s health. Elements made of cloth and paper that represented the brain, the healthy food, the junk food and physical and cognitive activity, were used. During the play, a neuroscientist explained to her friend (puppet) what the brain was and why it is important to keep it healthy. (2) We played a game of "magnetic fishing". The students had to "fish" from the ground images that represented everything that is good for "stimulating and taking care of" our brain: eating fruits and vegetables, riding a bike, skating, drawing, walking pets, hugging and avoiding things that hurt the brain: fighting, eating lots of goodies, watching a lot of television and getting angry. (3) We delivered a present that consisted of a card with a summary of what was learned and a healthy snack. This project was carried out in the context of Brain Awareness Week 2019 and funded by the Argentine Society for research in Neuroscience (SAN). The schools visited were: N°572 Doctor Rodolfo Freyre (Nelson); San José Obrero (Nelson); N° 1277 José Robustiano Aldao (Recreo) y Nuestra Señora de la Misericordia (Rafaela).

Brain Awareness Week Activities

P9.-Brain Awareness YEAR - 2019: PIs and PhD students visit 1K 4th-grade students across Córdoba with the 5-years-old activity "Neuroscience of he Senses"

María Constanza Paz[2], Nahir Guadalupe Gazal[1], Paula Virginia Subirada[2], Constanza Milena Jandar Paz[1], Alberto Leandro Oliveros[3], Andrea Guzman[3], Maria Victoria Vaglienti[2], Sebastian Miranda[1], Asier Angulo[1], Génesis D'aloisio[1,] Laura Gastaldi[5], Victoria Pisano[4], Cecilia Sánchez[2], Nicolas Unsain[1]
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Thanks to a grant from the Argentinean Society for Neuroscience Research (SAN) we participated in Brain Awareness Week 2019 with classroom activities in 4th grade. “Neuroscience of the Senses” explores the function of the brain with respect to the five senses by means of games and hands-on demonstrations. The project started with preparing the materials to take to the classrooms, the instructor´s manual and contacting recipient schools. 13 instructors were split in couples to reach classrooms of 20 elementary schools imparting more than 33 classes. The instructors were mainly advanced PhD students and PIs. Two instructors would arrive at their designated school with a box bearing all necessary materials and equipment for the class, which in some cases included carrying a microscope and a projector. Instructors were previously trained in group sessions with others prospective instructors and the help of a manual that also included a suggested script. The ultimate goal is to build a periodic activity for BAW and to help colleagues to repeat it in their cities. During the poster presentation we are going to share more details of the activity and the wonderful experience of interacting with the most curios creature in our galaxy: 10 years-old kids of H sapiens sapiens. This could not have been done without the help from SAN, INIMEC, MinCyT-Córdoba (Científicos con Vos y Voz) and CONICET-CCT/Córdoba.

Brain Awareness Week Activities

P10.-How much do you know about neuroscience? Did you know that neurons are not the most abundant cells in the brain? Let’s talk about glia

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Neuroscience is a rapidly expanding field of biology and medicine; however latest findings are not immediately available to the lay public. This project aimed to reach the community of Santa Rosa, La Pampa (where neuroscience is not a major research topic) to communicate and update them about glial cells. The grant obtained from the Argentinean Society for Neuroscience Research (SAN) in the context of Brain Awareness Week allowed us to travel from our laboratory in Buenos Aires to Santa Rosa. There, we conducted several activities related to science popularization in three major groups of the non-scientific community: high school students, university students (nursery and biology) and lay public. Day 1: Activities directed to high school students in Colegio Universidad de Santa Rosa involved practical activities interspersed with a minimum of theoretical concepts. Day 2: Lecture at the School of Biology and Agronomy of University of La Pampa (UNLPam), included research findings and experimental models followed by practical work using microscopes and histological brain samples (Nissl and immunohistochemistry). Day 3: In the main lecture hall of UNLPam, we conducted a lecture entitled “What are glial cells and why did Einstein´s brain have more of them?”. A very satisfactory outcome was achieved throughout all activities due to enthusiastic participation and interest from the very different audiences. In this poster, we will share our experiences with graphs and photographs.

Cellular and Molecular Neurobiology

P11.-Changes in the messenger RNA of the nicotinic receptor subunits in the aging mouse hippocampus

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Age is the main risk factor for a number of pathologies, including neurodegenerative diseases like Alzheimer, which is characterized by a loss of cholinergic neurons and impairment of the cognitive function. The physiological aging of the brain is encompassed by changes in different memory abilities. It is accepted that these alterations are related to deficient neuronal communication in absence of cell death. Therefore, alterations in the expression of the neurotransmitter receptors might be one of the causes leading to memory impairment with age. The most abundant nicotinic receptors in the brain are the α7 and α4/β2 pentamers, which are expressed in the hippocampus, cortex, limbic regions, thalamus and basal ganglia. These receptors have been shown to modulate the hippocampus-dependent learning and memory. We quantified the expression of the α7, α4 and β2 nicotinic subunits in the hippocampus of aging mice, using quantitative RT-PCR. We observed a significant reduction in the messenger RNA levels of the α7 and α4 subunits in 24-month old mice, compared to 3- and 12-month old mice. We did not detect significant variations in the messenger RNA amount of the β2 subunit in the aging animals. Immunohistochemical studies are needed to identify in which area and neuronal population of the hippocampus these receptor changes are taking place, in order to understand their relevance for the age-related memory loss.

Cellular and Molecular Neurobiology

P12.-Effects of ammonium on PC12 cells energy metabolism

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Hyperammonaemia can induce deleterious effects on the CNS and many mechanisms have been proposed to explain its toxic effects. Such mechanisms include alteration in neurotransmission and interference with energy metabolism. Previous studies from our laboratory showed that in a model of hepatic encephalopathy, mitochondria were important targets of NH4+-toxicity. The aim of this work was to study if calcium mobilization could be a mediator of the suggested mitochondrial dysfunction.We exposed undifferentiated PC12 cells to 0.5, 1 and 2 mM NH4+/NH3 during 24 hs. After cell loading with Fluo4AM and TMRE, flow cytometry, plate reader, and fluorescence microscopy were employed to measure (Ca2+)c and mitochondrial membrane potential respectively. The results showed that PC12 cells exposure to all the NH3/NH4+ doses, decreases (Ca2+)c after 1 min KCl-depolarization for both methods employed. In addition, the results obtained for the lowest NH4+/NH3 dose (0.5 mM) by flow cytometry and plate reader showed an 85% and 75% decrease in the (Ca2+)c respectively. The calcium decrease after 0.5 mM NH4+/NH3 was accompanied by a 13% of mitochondrial hyperpolarization, as compared with untreated cells. We conclude that NH4+/NH3 with its consequent alkalinization, were not able to activate extracellular Ca2+ entry after KCl depolarization. Our findings may contribute to the understanding of pathologic ammonium effects in different brain cells, and to the treatment of hyperammonemia.

Cellular and Molecular Neurobiology

P13.-Early and long-term effects of stress in male dorsal hippocampus: miRNAomics and behavioral relationship

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Neuroplasticity is a process that allows short to long-term brain remodeling in response to experiences and changing environment. This includes changes in synaptic remodeling and functional modification of neural circuitries. Acute and chronic stimuli (physical or emotional) triggers the activation of the stress system in which the acute stress allows organism to adapt; while chronic stress lead to a maladaptive response. Different animal models of stress show altered hippocampal-dependent behaviors; nonetheless, little is known about the molecular mechanisms involved. Considering that miRNAs play a key role in gene expression regulation, we evaluated the miRNA profile expression in dorsal hippocampus and the object location task in acute (2.5 h of restraint), acute recovery (24 h after stress) and chronic stress (2.5 h of restraint for 14 days). We showed that hierarchical clustering of miRNA expression profile shows a similarity between acute and chronic stress. Consistently, acute and chronic stressed animals showed a decrease preference to explore an object in a novel position. Interestingly, acute recovery group displayed not only a similar miRNA profile, but also a similar preference for novel location both compared to controls. The enrichment analysis predicts functional relevance of miRNA roles in modulation of signaling pathways related to cell survival, protein metabolism, inflammation, during the transition between acute and chronic stress.

This work was supported by FONDECYT 119-0899 and ENL0118-01

Cellular and Molecular Neurobiology

P14.-Ghrelin system regulates neurons of the supramammillary nucleus

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Ghrelin is a stomach-derived hormone that acts via the growth hormone secretagogue receptor (GHSR) and regulates a variety of physiological functions. GHSR is expressed in the supramammillary nucleus (SuM), a hypothalamic area involved in behaviors associated with food intake, food-reward and novelty. However, the effects of ghrelin in the SuM are uncertain. Here we used mice, in which the enhanced green fluorescent protein

(eGFP) is expressed under the control of the GHSR promoter (GHSR-eGFP mice), to gain neuroanatomical and functional insights of the GHSR neurons of the SuM. First, we validated the GHSR-eGFP mice as a reporter model for GHSR neurons in the SuM. We found that GHSR-eGFP mice contain a ~ 400.39±20 eGFP+ cells in the SuM, and that ~53.19 % of them express GHSR. In GHSR-eGFP mice, we found that GHSR neurons of the SuM do not produce GABA or dopamine. In wild-type mice, we found that systemic administration of ghrelin, fasting and fasting-induced refeeding do not induce increase of the marker of neuronal activation c-Fos in the SuM. In contrast, intra-VTA-injected ghrelin, high-fat diet bingeing eating, and caloric restriction increase of c-Fos levels in the SuM. Thus, current data suggest that GHSR signaling activates neurons of the SuM under specific experimental conditions.

Cellular and Molecular Neurobiology

P15.-Perinatal protein malnutrition results in genome-wide disruptions in hippocampal 5-hydroxymethylcytosine at regions that can be rescued by an enriched environment

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Maternal malnutrition remains one of the major adversities affecting newborn brain development and long-term mental health outcomes. Perinatal protein malnutrition increases the risk to develop anxiety-like behavior. Studies in mice have shown that these altered behaviors can be rescued by enriching the growth environment. The epigenetic mark 5-hydroxymethylcytosine (5hmC) is an environmentally sensitive DNA modification that is highly enriched in the brain and is associated with gene expression. Here, we examined 5hmC distribution throughout the ventral hippocampus of female mice exposed to a low protein diet (8% casein) or normal protein diet (20% casein) during gestation and lactation and that were assigned to different environmental paradigms after weaning: normal or enriched environment (i.e., social and sensory stimulation). We observed 508 differentially hydroxymethylated regions (DhMRs) associated with protein malnutrition and that an enriched environment rescued the hydroxymethylation levels at a significant number of these regions (N = 52; p-value < 0.01), including on neurologically related genes such as Nrp2, Ntm, Nav1, Sox6. Sequence motif predictions indicated that 5hmC may regulate gene expression by mediating transcription factor binding of these transcripts. Together, these findings represent a critical step toward understanding the molecular effects of the environment on the mechanisms that underlie anxiety disorders.

Cellular and Molecular Neurobiology

P16.-Cholesterol recycling is altered during aging in nervous system cells

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The NPC1 (Niemann Pick C1) protein is strictly required for intracellular cholesterol redistribution in most eucariotic cells. Mutations in genes NPC1 leads to a rare autosomal recessive, lysosomal and multisystemic neurodegenerative disease. Data obtained in our laboratory show that NPC1 levels are reduced in the hippocampus of old mice (20 months) suggesting that the loss of neuronal function during aging could be due, at least in part, to the fact that old neurons have an Niemann Pick phenotype.
These data were reproduced in vitro in an accelerated aging model, obtained by treatment of astrocytes, primary neurons or cell lines with D-galactose. Using this model we have also analyzed the accumulation and localization of a cholesterol analog tagged with a fluorescent probe called BODIPY-Cholesterol. Our results suggest that the NPC1 decay that occurs during aging leads to intracellular cholesterol accumulation. Furthermore, npc1 decrease seems to be epigenetically regulated by HDAC2 enhanced activity. Indeed the levels of sphingosine kinase 2 (SPHK2), a protein involved in HDAC2 inhibition are also reduced in old neurons and in D-gal treated cells. Pharmacological inhibition of Sphk2 resulted in NPC1 decreased expression and BODIPY-cholesterol accumulation.

Cellular and Molecular Neurobiology

P17.-First insights into cell signaling modulation in neuronal SH-SY5Y cells induced by Yerba Mate.

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Ilex paraguariensis (Yerba mate [YM]) is a very popular beverage in South America. Epidemiological evidences suggest that YM is beneficial for human health disorders, such as diabetes, obesity and Parkinson's disease. In line with this latest, our group demonstrated that administration of YM extract in primary mesencephalic cultures provides survival to dopaminergic neurons, those primarily affected in Parkinson´s disease. The objective of the current work is to investigate the molecular mechanisms triggered by exposure to YM extract which may ultimately explain neuronal survival. The first aim presented herein is the regulation of key molecular markers of the human neuroblastoma SH-SY5Y cells under YM treatment. We have treated SH-SY5Y cells with different concentrations and at different time points of YM. We found that YM treatment has a mitogenic but not differentiated effect on this cell line. Moreover, we measured the protein levels and phosphorylated status of key elements of energy signaling and autophagy (AMPK and p70S6Kα), mitogenesis and differentiation (EGR-1) and the multifaceted ERK protein by Western Blot. We found that YM upregulated both pERK and pAMPK, the last one in a time dependent manner. On the contrary, YM downregulated EGR-1 levels and had a mild effect on p-p70S6Kα. These initial results suggest that YM has a role in cell energy homeostasis and/or autophagy but much further work is still necessary to confirm, interpret and translate our findings.

Cellular and Molecular Neurobiology

P18.-Novel molecular mechanisms associated with impaired peripheral nerve repair mediated by anti-ganglioside antibodies

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Guillain Barré Syndrome (GBS) is an acute monophasic polyneuropathy characterized by the presence of ascending muscular paralysis and arreflexia. In a subgroup of patients, paralysis is related to the presence of high titers of antibodies targeting gangliosides (anti-Gg). Passive transfer studies with a mAb anti-Gg (anti GD1a-GT1b, clone 1b7) in a murine model of axon regeneration confirmed that these antibodies are able to inhibit nerve repair by negative modulation of actin and tubulin cytoskeleton in growth cones. In vitro studies demonstrated that this effect is mediated through the activation of RhoA/ROCK dependent and independent signaling pathways. However, recent findings in this model show that nerves from animals exposed to anti-Gg display a significant failure in the clearance of tissue debris, suggesting a possible effect on non-neural cells. Chronic administration of a pharmacological inhibitor of the RhoA/ROCK pathway, Y-27632; was able to reverse this effect. Experiments display that mice treated with mAb 1B7 show a reduced number of macrophage extravasation/migration in sciatic nerves respect to control nerves. Furthermore, in vivo experiments highlight the role of anti-Gg in the modulation of macrophage phenotype. Circulating macrophages and sciatic nerve extravasated macrophages showed a M2 like phenotype in mice treated with anti-Gg compared with control. In conclusion, these results suggest the effect of anti-Gg on nerve repair by targeting non-neural cell.

Cellular and Molecular Neurobiology

P19.-TNFR1a as a transducer molecule for the inhibitory effect of anti-ganglioside antibodies on axon regeneration

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Guillain Barrè Syndrome (GBS) is an acute autoimmune polyneuropathy where anti-ganglioside antibodies (anti-Gg Abs) are associated with poor clinical recovery. Anti-Gg Abs exert inhibition of axon regeneration via activation of RhoA/ROCK/CRMP-2 signaling pathways, but the identity of their transducer molecule remains obscure. Based on a proteomic study searching ganglioside interacting proteins and the use of an shRNA-based screening, we identified tumor necrosis factor receptor 1A (TNFr1A) as a transducer protein for the inhibitory effect on neurite outgrowth of an anti-Gg mAb targeting GD1a/GT1b. Silencing TNFr1A abolished the inhibitory effect of anti-GD1a mAb but not anti-GT1b specific mAb on Dorsal Root Ganglion neurons (DRGn), showing specificity on the interaction. These results were confirmed using DRGn cultures from TNFr1A-null mice and the use of an in vivo model of axon regeneration by comparing wild type and TNFr1A-null mice. Interestingly, lack of TNFr1A expression in DRGn abolished the ability of anti-GD1a mAb to activate RhoA pathways. We also identified the pertussis toxin-sensitive guanine nucleotide-binding protein G(i) subunit α-2 as part of the signaling cascade triggered by anti-Gg Abs. We developed mutant forms of TNFr1A at the extracellular stalk region to identify the site of interaction.

Cellular and Molecular Neurobiology

P20.-The neddylation pathway modulates cytoskeletal actin dynamics altering neuronal development

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Neuronal development is controlled by signaling cascades regulated by a myriad of posttranslational modifications. Although the role of ubiquitin has been well established in the maturation of nerve cells, the function of other members of the ubiquitin-like protein family remains poorly understood. Nedd8 is the UBL with the highest homology to Ub, and we saw that Neddylation is highly abundant in the brain and is critical for synapse formation and maintenance. Blocking Neddylation with genetic and pharmacological tools reduced axonal and dendritic growth both in cell culture and in-utero electroporation approaches. These effects were partially reverted by Cyto-D and Taxol. These results suggest that cytoskeleton dynamics are involved in the effects of Nedd8 on axodendritic growth. To identify the structural details underlying the effects of Nedd8 we employed superresolution, and fluorescent microscopy. Neddylation blockade with MLN4924 strongly reduced microtubular invasion, induce ectopic lamellipodia formation and increased the growth cone size in early neurons. In biochemical screenings, we have identified several neddylated targets that are regulators of cytoskeleton structure and function, such as cofilin. We evaluated the function of neddylation on cofilin performing molecular replacement strategies and found that the disruption of cofilin neddylation produced a reduced cellular F/F+G actin ratio, impair axon growth and reduced dendritc growth and arborization.

Cellular and Molecular Neurobiology

P21.-Redox imbalance in retinal degeneration promoted by constant ligh exposure

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The overexposure to light, called Light Pollution, may be one of the many factors that can induce the interruption of retinal homeostasis, promoting the injury of this tissue by retinal cell death that results in retinal degeneration (RD).
Previously, we demonstrated that constant exposure to white LED light (200 lux) affects outer nuclear layer (ONL) trigger rods and cones cell death, an increase in rhodopsin phosphorylation and significant changes in Melanopsin and Neuropsin expression and localization in the inner nuclear layer and ganglion cell layer. Therefore, to further studying the molecular pathways of RD, we have examined cellular redox state and fatty acid composition in rat retinas constantly exposed to light. We demonstrated an increase in H2O2 after 5 days; however, catalase activity did not show significant differences in all times studied. Fatty acid composition analysis showed that docosahexaenoic acid (DHA) decreased after 4 days. Remarkably, DHA diminution showed a positive correlation with the rise in stearic acid indicating a possible association between them. We assumed that the reduction in DHA may be affected by the oxidative stress in photoreceptors outer segment which in turn affects the stearic acid composition with consequences in membrane properties. All these miss-regulation affects the photoreceptor survival through unknown mechanisms involved. We consider that oxidative stress might be one of the pathways implicated in RD promoted by light.

Cellular and Molecular Neurobiology

P22.-Cognitive impairement and changes in hippocampal plasticity genes in the transgenic McGill-R-Thy1-APP rat model of Alzheimer´s disease

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McGill-R-Thy1-APP Wistar-transgenic (Tg) rats, bearing human amyloid precursor protein with Swedish and Indiana mutations of familial Alzheimer's disease (AD), are suitable for testing learning and memory at AD onset. Homozygous Tg rats showed cognition deficits at 3 month old (mo); human amyloid-β (Aβ) accumulates from 1st week, developing extracellular amyloid pathology in 6 mo animals. Hemizygous (He) rat does not develop extracellular plaques even at 20 mo. When 3, 4 and 6 mo He male rats and their wild-type litter-mates (WT) were left to explore an open field (OF) for 5min and were tested 24h later (long-term-memory, LTM), denoted habituation to the environment. Same He and WT rats were trained for object recognition (OR) and inhibitory avoidance (IA) to a mild foot-shock. All groups discriminated new versus known object 1h later (short-term-memory), but 4 and 6 mo He rats did not show OR-LTM neither IA-LTM. Some plasticity genes were analized in the hippocampus ofHe compared with WT 4mo male rats. There were no significant differences for PSD95, Arc, GluR1 AMPA receptor or NR1- and NR2A-NMDA receptor subunits; while NR2B and CaMKIIb mRNA levels were significantly higher, suggesting an expression increase. These results strongly suggest that deficits in associative LTM develop at about 4 mo and that there is an increase in hippocampal expression of CaMKIIb and NR2B, likely due to intracellular Ca2+ rise following NMDA receptor overstimulation by Aβ oligomers.

Cellular and Molecular Neurobiology

P23.-APP/Go signaling modulates the interaction between APP and BACE1

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The amyloid beta (Aβ) deposition in the brain has a key role in the etiology of Alzheimer´s disease. The encounter of amyloid precursor protein (APP) and BACE1 is the most critical event in amyloidogenesis. The factors modulating this event are poorly understood but there is crescent evidence about the importance of endosomal sorting of both proteins. Also, some evidence suggests that Aβ is capable of induces its own production in a feed-forward fashion, but the mechanism is yet unclear. We hypotetized that this mechanism implies a change in the intracellular distribution of APP and BACE1, and that depends on Aβ interaction with APP and its signaling pathway mediates by Go/βγ. We found that treatment with Aβ was able to increase the colocalization of APP and BACE1, in soma and processes of hippocampal neurons. This effect was avoided by a pretreatment with gallein, an inhibitor of βγ complex. Also, we found that this increase occurred in recycling endosomes as both proteins incremented its colocalization with Rab11. Moreover, overexpressing a system of bimolecular fluorescence complementation (APP-Vn /BACE1-Vc) we found an increase in the degree of interaction between both proteins in N2A cell cultures induced by both, oligomeric and fibrilar Aβ. This effect

was avoided by a pretreatment with gallein. In conclusion, Aβ induces an increment in the colocalization and interaction of APP and BACE1 in recycling endosomes which is dependent of Go/βγ signalling.

Cellular and Molecular Neurobiology

P24.-Localization of the tyrosine hydroxilase positive cells with the prosomeric model in hypothalamus of postnatal rats

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Tyrosine hydroxylase (TH) is the rate limiting step in the synthesis of catecholamines. The expression of TH in the hypothalamic territory is mainly related to cells around the arcuate nucleus in the acroterminal domain. We aimed to analyze in detail the TH/Th expression in hypothalamic domains and subdomains Sprague Dawley rats at postnatal stages (P56 and P100). Combined immunohistochemistry and in situ hybridization for TH/Th on the same sections were compared with markers of specific hypothalamic nuclei (Pomc, Agrp, Avp, Oxt, Crh, Trh and Sst mRNA expression) in consecutive sections. In the paraventricular and subparaventricular alar domains Th/TH positive cells are most abundant within the periventricular layer at the level of the terminal portion, where some Th positive cells also can be observed in the intermediate layer, but such neurons are practically absent at the acroterminal portion and only a few are present in the peduncular subregion. In the tuberal basal region most labeled cells are found in the neighborhood of the medial eminence (mainly arcuate nucleus), in the acroterminal domain, but some cell groups can be detected as well in the peduncular retrotuberal region, including the A13 cell group, as found in the mouse. The prosomeric model was an excellent tool to determine precise localization of the Th/TH positive cells, a population that integrates into complex hypothalamic functions.

Cellular and Molecular Neurobiology

P25.-GM1-pentasaccharide (osGM1) prevents damage on dopaminergic system in a mouse model of Parkinson's disease

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Glycosphingolipids (GSLs) are components of most cell membranes and are particularly abundant in the nervous system. GSLs play important roles in neuronal development and survival and modulate a variety of cell activities. Several mechanisms have been proposed to explain the biological effect of GSLs, although a complete understanding of them is still missing. Exogenously administered GSLs (gangliosides in particular) have been clinically tested for treatment of several diseases and it has been demonstrated that short-term use of monosialoganglioside GM1 resulted in significant symptoms reduction in Parkinson's disease (PD) patients. In

vitro and in vivo experiments showed that GM1 exerts neurotrophic functions by interacting with plasma membrane proteins through its oligosaccharide portion (osGM1). We investigate the response of the damaged dopamine system to osGM1 in the neurotoxin 1-methyl-4-phenyl-1,2,3,6-terahydropyridine (MPTP)-induced model of PD in mice. osGM1 was intraperitoneal injected (30.0 mg/kg) to young C57/BL6J mice with severe striatal dopamine depletion (approx 90%) caused an increase in striatal dopamine levels. This effect was not apparent at a higher dose (60 mg/kg). These results show that osGM1 can partially restore striatal dopamine levels in MPTP-treated mice. osGM1 may lead to the development of new types of useful neuroactive compounds for Parkinson's disease treatment.

Cellular and Molecular Neurobiology

P26.-Serotonin (5-HT) and catecholamines (CA) coordinates antagonistic food-related behaviors in C. elegans.

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Despite the intermodulation between serotonergic and adrenergic signals is crucial throughout the animal kingdom, the molecular and cellular mechanisms underlying this interrelation are poorly understood. We here use C. elegans as a model to get insights into the neural circuits linking 5-TH and CA.
When food-deprived worms encounter food, 5-HT is released to slow-down their locomotion and to stimulate pharyngeal pumping.In contrast, exogenous Tyramine (TA) and Octopamine (OA), invertebrate counterparts for adrenaline and noradrenaline, stimulate locomotion and decreases pharyngeal pumping. We found that tdc-1 mutants (unable to synthesize TA and OA) are hypersensitive to 5-HT-mediated paralysis, suggesting that TA and OA acts antagonistically to 5-HT. We also identify the TA (TYRA-3) and OA (SER-3 and SER-6) receptors involved in this antagonism. Moreover, our calcium imaging recordings showed that the peak of activity of serotoninergic neurons upon encountering food is significantly higher in tdc-1 null mutant background. Taken together these results suggest that TA and OA counteract serotoninergic signaling by driving opposing behaviors and by inhibiting 5-HT release. Our final aim is to decipher the neural circuit and the molecules involved in the reciprocal modulation between CA and 5-HT in C. elegans. Given the conservation in molecular components of these pathways, our studies are likely significant to understand this interrelation in other animals.

Cellular and Molecular Neurobiology

P27.-Tyrphostin AG879 and c-Src inhibitors reduced neurite outgrowth induced by stimulation of Ang II AT2 receptors in SH-SY5Y neuroblastoma cells.

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SH-SY5Y is a neuroblastoma cell line used as model of Parkinson disease, Alzheimer and differentiation. The signaling mechanism of neurite outgrowth induced by Ang II AT2 receptors and the interaction with NGF receptors remains unclear. We evaluated neurite outgrowth under differentiation conditions in SH-SY5Y cells, in the presence of different inhibitors: UO126 (MEK inhibitor), LY294002 (PI3K inhibitor) and PP2 (c-Src inhibitor). Only PP2 was able to reduce neurite outgrowth induced by the AT2 receptor´s agonist CGP42112A, supporting

the role of c-Src in the signaling pathway, without participation of MAPK or PI3K. Activation of c-Src was confirmed by phosphorylation at residue Y416, a rapid response, followed by Y416 dephosphorylation and Y527 phoshorylation (deactivation of c-Src), suggesting a physiological response. The expression level of Ang II AT2 receptors increased with differentiation, induced by stimulation with CGP42112A, RA or NGF. We evaluated the participation of the TrkA receptor, by using AG879, a specific inhibitor. AG879 clearly inhibited neurite outgrowth, following stimulation with either Ang II or CGP42112A. Taken together, this observation with the effect of CGP42112A in neurite outgrowth induction and increased expression level of AT2 receptors following neurodifferentiation, these results suggest an interaction between both receptors, AT2 and NGF. We further identified the participation of c-Src as a key player in the signaling pathway.

Cellular and Molecular Neurobiology

P28.-Impact of Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene in the vulnerability to cocaine addiction induced by chronic stress

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The main goal of this project is to evaluate the influence of a single-nucleotide polymorphism (SNP) on the brain-derived neurotrophic factor (BDNF) gene leading to a valine (Val) for methionine (Met) substitution (Val66Met) in the BDNF prodomain in a model of cross sensitization between stress and cocaine. This SNP has been associated with mood disorders, stress and drug abuse in the human carriers. However, the underlying circuitry and mechanisms involved remains cryptic. We will use BDNF Val/Val and BDNF Met/Met knock-in mice to assess the impact of this SNP on the vulnerability to develop stress-induced cocaine addiction. First, we will evaluate possible behavioral differences between genotypes generated in response to stress and cocaine. Then, we will evaluate molecular and structural changes in the two subdivisions of nucleus accumbens (NA), core and shell, in mice from both genotypes under this stress-cocaine association protocol. Interestingly, it has been described that the Val66Met polymorphism of the BDNF prodomain causes an alteration in the regulation of Rac1 activity. Rac1 is involved in the regulation of the actin cytoskeleton dynamics in dendritic spines and in neuronal plasticity induced by cocaine. Thus, we hypothesized that the Met variant of the BDNF prodomain alters the NA structure through the dysregulation of Rac1 activity and we propose this could be a mechanism that contribute to the vulnerability to sstress-induced cocaine addiction.

Cellular and Molecular Neurobiology

P29.-Heterogeneity of effects of antipsychotic drugs on voltage-gated calcium channels type 2 (CaV2.2) currents

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Antipsychotic (APs) are a heterogeneous group of drugs widely used in the treatment of schizophrenia (SCZ), but the molecular basis of their effects in neurons are not fully understood. CaV family is critical for controlling calcium influx in neurons, thus modulating transcription (CaV1), neurotransmission (CaV2) and electrical activity (CaV3). Moreover, localization, genetic variations and function of CaV are associated with SCZ and some APs function as CaV1 and CaV3 blockers. In this work, we evaluated the effects of three different APs on CaV2.2 currents. We selected two typical (haloperidol and chlorpromazine) and one atypical (risperidone) APs with different chemical structures and diverse physiological effects. We transfected HEK293T cells with CaV2.2 and its auxiliary subunits and recorded calcium currents by voltage clamp. We evaluated the effect of increasing concentrations of APs on CaV2.2 current levels. We performed dose-response curves for each AP and found dissimilar effects. Haloperidol and risperidone acutely inhibited CaV2.2 currents. However, CaV2.2 currents were considerably more sensitive to haloperidol compared to risperidone. On the contrast, chlorpromazine showed no effect on CaV2.2 currents. These and future experiments will allow us to understand the role of calcium channel modulation by APs related to the high diversity of neuronal effects shown by these drugs.

Cellular and Molecular Neurobiology

P30.-Maternal stress alters BDNF signaling expression in hippocampus and reduces anxious-like phenotype in prepubertal offspring rat

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Prenatal stress (PS) affect offspring brain plasticity increasing risk to develop stress-related disorders. Brain-derived neurotrophic factor (BDNF) regulates neural development; it alteration is linked with the incidence of neuropsychiatric disorders. Here, we assess PS consequences on the expression of BDNF signaling in the hippocampus, and if such changes are linked with anxious-like phenotype. The expression of candidate genes related to DNA methylation pathway and global DNA methylation levels were further evaluated. Wistar rats received restraint stress during the third week of gestation or left undisturbed (control group, C). Anxiety-like behavior was tested by EPM and dark/light box starting at postnatal day 25. After behavioral test ended, hippocampi were processed for Rt-PCR or DNA dot blot assays. PS offspring show reduced anxiety-like behavior and increased mRNA levels of bdnf exon iv and crhr1. Sex differences were found on PS induced changes for bdnf receptors mRNA levels: trk2b expression was decreased in male, while ngfr and truncated-trk2b were increased in female pups. In males, PS increased mRNA levels of chromatin remodeler genes and reduced global methylated DNA content. Our results show that PS altered hippocampal gene expression and modulate offspring anxious phenotype. In males, such changes could be mediated by epigenetic changes. On-going studies are performed to explain the functional relationship between these outcomes.

Cellular and Molecular Neurobiology

P31.-Retinal degeneration promoted by excessive light: Role of the Glial cells

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Excessive exposure to artificial light affects the retina inducing photoreceptors cell death and leading to retinal degeneration (RD). Previously, we have established a novel model of RD by exposing adult rats to constant low intensity LED lights (200 lux). Using this model we showed that, after 5 days of exposure, the retina suffers important structural changes including photoreceptors cell death, opsins re-localization and increased oxidative stress. In the present work, we aimed to understand the role of neuroinflammation in the RD promoted by light excess; thus, we assessed the time course of glia activation after 2, 4, 6 and 8 days of constant light exposure. Retinas were processed either for western blotting (WB) or IHC and we evaluated GFAP expression (Müller cells) and Iba-1 expression (microglia marker). After 4 days of exposure, we observed a significant increase of active microglial cells (ameboid-shaped) and also, the active microglia relocated towards the outer retina (next to rods and cones nuclei). At the same time-point, we observed strong Müller cells activation compared to controls. Interestingly, WB analysis of the same retina revealed the appearance of breakdown GFAP products (GFAP-BDPs), a proposed biomarker for Central Nervous System injury at two days exposure. Thus, our results indicate that glial activation precedes the photoreceptors cell death and suggest that an inflammatory response may be inducing cell-death pathways in our RD model.

Cellular and Molecular Neurobiology

P32.-A cell-based model for αS aggregation in Parkinson disease: Testing the correlation between structural and cellular biology

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The discovery of aggregation inhibitors and the mechanism elucidation are key in the quest to mitigate the toxic consequences of amyloid formation. Previous studies of the antiamyloidogenic mechanism of action of sodium phtalocyanine tetrasulfonate (PcTS) on α-Synuclein (αS), demonstrated that specific aromatic interactions are fundamental for the inhibition of amyloid assembly. Here we studied the influence of structural modifications on the activity of tetrapyrrolic compounds on αS aggregation. For the first time, our laboratory has extended the studies in the field of the bioinorganic chemistry and biophysics to cellular biology using a well-established cell-based model to study αS aggregation. Binding modes of the tetrapyrrole ligands to αS are determined by the planarity and hydrophobicity of the aromatic ring system in the tetrapyrrolic molecule and/or the preferential affinity of the metal ion conjugated at the center of the macrocyclic ring. The different capability of these compounds to modulate αS aggregation in vitro was reproduced in cell-based models of αS aggregation, demonstrating unequivocally that the modulation exerted by these compounds on amyloid assembly is a direct consequence of their interaction with the target protein.

1. Gonzalez N, Gentile I, Garro HA, et al. Metal coordination and peripheral substitution modulate the activity of cyclic tetrapyrroles on αS aggregation: A structural and cell-based study. J Biol Inorg Chem. 2019.In Press.

Cellular and Molecular Neurobiology

P33.-Sera from prediabetic patients induce changes in neurons and glia in mix primary cultures

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Different studies performed in human patients, animal models, and in vitro in cell cultures, show a correlation between type 2 diabetes (DBT2) and certain neurodegenerative pathologies. However, molecular and cellular mechanisms that link both conditions have not yet been demonstrated. Several works suggest that inflammation, cellular stress and RAGE mediated signaling pathway could be associated with neurodegenerative damage related to DBT2. Currently, there are few data about changes in central nervous system during the period prior to DBT2, known as impaired glucose tolerance (IGT). For this reason, we modeled a prediabetic condition in vitro, exposing hippocampal mixed cultures of neurons and astrocytes to sera from IGT and control patients. In these conditions, we studied morphological differences present in both cell types, as well as differences in astrocyte number and morphology.We found that acute treatment (1 hour) with sera from IGT patients induce cellular stress. Furthermore, 7 days treatment induces changes in astrocytes number and shape as well as a decrease in neuron number. Both the increase in astrocyte and the reduction in neurons percentage correlate with glucose levels. These preliminary results would lead us to hypothesize that the increase in glucose values could start changes in neurons and glia that are compatible with neurodegeneration.

Cellular and Molecular Neurobiology

P34.-MAG as a therapeutic target for neurodegenerative diseases associated to glutamate overload

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The aim of our work is to study the protective effect of oligodendrocytes (OLs) against glutamate (Glu) overload, focusing on their key role as critical modulators of extracellular glutamate (eGlu) in white matter. Our group has previously described that mAb-mediated crosslinking/activation of MAG triggers a phosphoinositides/PKC-dependent intracellular signaling which results in reduced oxidative stress and protection of OLs and nearby neurons against Glu overload. By using a fluorometry-based technique we confirmed that long term antibody-mediated activation of MAG triggers eGlu uptake by OLs. In the hunt for novel therapeutic bioactive ligands of MAG derived from the structure of its axonal receptors, we tested soluble chimeric forms of its receptors in their ability to trigger an increase in reduced glutathione (GSH) content, evidenced by staining of OLs with the dye monochlorobimane. We tested commercially available IgG Fc fragment-bound chimeras of receptors NgR1, LRP1, PirB and synthetized covalently-linked ganglioside GT1b-BSA derivatives. GT1b-BSA induced a potent increase of GSH by OLs, while no effect was observed with the structurally-related ganglioside GM3-BSA complex, carrying the common epitope sialyl(α2-3)Gal terminal residue. A weak eGlu uptake was observed when testing other soluble receptors. Altogether, these studies can contribute to the development of novel neuroprotective therapies in order to mitigate neurodegeneration associated with Glu toxicity.

Cellular and Molecular Neurobiology

P35.-TDP-43 overexpression affects global brain translation

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TDP-43 is a RNA-binding protein that, amongst other functions, participates in mRNA metabolism, and it is a major component of inclusions observed in neurodegenerative diseases like frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Previous results from our lab showed a decrease in global mRNA translation as compared to wild-type animals, revealed by polysome profiling of brain cortex from hTDP-43 expressing mice. To further understand the role of TDP-43 in mRNA and protein metabolism, we used a combined approach with animal and cellular models. Application of SUNSET method (which assesses ongoing translation) in brain slices from control and hTDP-43-ΔNLS expressing mice revealed a decrease in puromycin incorporation in brain cortex cells of ΔNLS mice when compared to control animals. Complementary immunoblot analysis corroborates that puromycin is actively incorporated during translation of new proteins. The Unfolded Protein Response (UPR) is a major cellular process that also regulates translation. To assess in vitro how TDP-43 modulates the UPR, HEK293 cells were transfected with TDP-43 variants and treated with vehicle or ER stress inducers. We are currently analyzing ATF4 and ATF6 pathways; preliminary data corroborate that MG132 induces ATF6 cleavage and ATF4 protein levels. These results suggest that dysregulation of TDP-43 might alter global translation and that cytotoxic effects in FTD/ALS might be due to alterations in proteostasis by TDP-43.

Cellular and Molecular Neurobiology

P36.-Astrocyte conversion to proinflammatory-neurodegenerative phenotype is a key step in evolution of traumatic brain injury

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Reactive gliosis characterizes astroglial response to brain injury. The mechanisms that propagate reactive astrogliosis and facilitate neurodegeneration are not fully understood. It has been proposed that core-derived DAMP have a major role in the reactive astrogliosis propagation and neurodegeneration. However, in silico modeling has shown that DAMP release does not justify the experimental findings (Auzmendi et al.,Mol. Neurobiol 2019). Using a model of traumatic brain injury (TBI) by stab wound in C57BL/6 mice and reconstituted glial cultures from TLR2KO mice, we here aimed to understand the role of TLR2 and downstream NFkB activation in reactive gliosis and neurodegeneration. Animal motor deficits were analyzed by computer-assisted open field. Our results showed that TBI induces reactive gliosis that propagates from the injury to distal brain, with a maximal reactivity at 7 days post TBI (DPI). This time point also showed significant neurodegeneration and neurological deficit. NFkB blockage with 150 mg/kg sulfasalazine reduced reactive gliosis without showing neurological improvement; while TLR2KO mice presented increased reactive gliosis but better performance on open field at 7DPI. In vitro reactive gliosis is exacerbated in TLR2KO astrocytes cocultured with wild type

microglia. We conclude that reactive gliosis does not necessarily parallel with neurological outcome, being the proinflammatory-neurodegenerative polarization a key step in the evolution of the TBI.

Cellular and Molecular Neurobiology

P37.-Subcellular localization of Angiotensin II receptors in Substantia nigra of young and aged rats.

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Aging is a prominent risk factor for Parkinson and neurodegenerative diseases.The Renin-Angiotensin-System (RAS) regulates multiple physiological functions, activating Angiotensin II (Ang II) type 1 (AT1) and type 2 (AT2) receptors. The presence of both Ang II receptor subtypes have been described in the Substantia nigra (SN). Ang II AT1 receptors might cause oxidative stress and contribute to neurodegenerative process. We evaluated age-dependent variations of Ang II receptor immunolocalization in SN (14 µm sections), in young (P21) and aged (P365) male rats, by using specific anti-AT1 and anti- AT2 antibodies. Young animals evidenced a higher number of AT2 positive cells than AT1 immunolabeled cells (38% vs 12% respectively). In aged rats a lower density of labeled cells was observed for both, AT2 (13%) and AT1 (8%) receptors. AT1 receptors were observed in large cells, which resemble pigmented cells and localized intracellularly, mainly in a perinuclear localization.Besides, AT2 receptors showed cytoplasmic and perinuclear localization. The perinuclear localization agrees with previous reports ofmitochondriallocalization. The total number of immunoreactive cells (AT1 and AT2) diminishes at P365, thus suggesting that the cell lost is a consequence of aging. The diminished number of immunopositive cells might account for the effect of age-related changes in the RAS while the localization might explain the high sensitivity of SN neurones to oxidative stress.

Cellular and Molecular Neurobiology

P38.-Sexual dimorphism in the effect of glucocorticoids on the miRNA expression pattern in rat hippocampus

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Glucocorticoids (GCs) through several mechanisms regulate a myriad of cellular processes, including miRNAs expression. The hippocampus, a key structure in learning and memory, is an important target due to enrichment of glucocorticoid (GR) and mineralocorticoid (MR) receptors. Evidences suggest that GCs in hippocampus inhibit the proliferation of neural progenitors and promote the survival of neurons. Interestingly, although males and females share a common genome, in vitro and in vivo non-neural models have described that miRNAs levels are altered in a sex-dependent manner by GCs. Considering that miRNAs are key regulators of gene expression at post-transcriptional level, we evaluated if corticosterone (CORT) differentially regulates miRNA expression in

female and male adrenalectomized rat hippocampus using a Microarray platform. To predict the role of CORT in miRNA regulation, we performed in-silico analysis of the putative promoter regions and its interaction network of validated target mRNAs. We found that CORT induced a sex-biased miRNA expression profile in rat hippocampus. Additionally, in-silico promoter analysis suggests that neither GR nor MR would directly regulate miRNAs expression; instead, it would be through indirect mechanisms e.g. interaction with other transcriptional factors. Finally, validated target mRNAs analysis also indicated a sex-biased effect of CORT. These results suggest that miRNAs could modulate neurogenesis, proliferation and apoptosis.

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P39.-Revealing the long-range three-dimensional organization of tanycyte processes within the basal hypothalamus of mice

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Hypothalamic tanycytes are specialized ependymal cells that line the ventral part of the third ventricle and emit processes into the basal hypothalamus. These cells are involved in a host of functions, including energy homeostasis, nutrient sensing, and hormonal transport and regulation. Here, we present a novel approach to study the anatomical distribution and fine architecture of the processes of the hypothalamic tanycytes in mice. The ependymal walls were labeled, including tanycytes and their processes, using an intra-cerebroventricular injection of an adenoviral vector expressing GFP (RAd-GFP). Then, consecutive brain slices were obtained using a standard cryotome and sequentially mounted for fluorescence volume imaging. Tanycyte morphology with fine structural detail was readily labeled and observable in the z-stacks obtained. Continuous volume reconstructions spanning several hundreds of microns were achieved using a software tool that we developed for the open source package Fiji. This elastic alignment technique was able to overcome the deformation introduced by sample slicing, by matching corresponding features in adjacent slices. With this procedure, we were able to map the distribution and orientation of tanycytic processes throughout the sampled volume, as well as to identify and map their contacts with the hypothalamic vasculature. This approach provides a valuable tool to study the complex relationship of hypothalamic tanycytes and their surrounding parenchyma.

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P40.-A circular RNA derived from the Tulp4 gene controls excitatory neurotransmission and regulates anxiety-related behavior

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Exonic circular RNAs (circRNAs) are a recently characterized class of noncoding RNAs. These molecules derive from exonic sequences and are generated by an alternative mechanism of splicing known as backsplicing, which yields a single-stranded RNA molecule with covalently joined ends. Due to their recent identification, the function of circRNAs is still almost unexplored. We have recently accomplished a systematic high throughput identification of numerous circular transcripts derived from nerve tissue samples. From these data, we have selected a circular RNA transcript derived from the Tulp4 (Tubby-like protein 4) gene to perform a functional characterization. We observed in loss-of-function experiments, both in primary neurons and in brain slices, that circTulp4 regulates excitatory neurotransmission and affects the number of glutamatergic synaptic contacts.
To study the role of circTulp4 in vivo, we have generated a transgenic knock-out mouse line mutating a splicing acceptor site using CRISPR/Cas9 technique. Preliminary results show that mice lacking circTulp4 have impaired neurotransmission, have changes in the protein composition of synaptic compartments and exhibit behavioral alterations including working-memory deficits and increased anxiety.

Cellular and Molecular Neurobiology

P41.-Development of a regulable system for neuronal specific molecular silencing using micro RNA for therapeutical purposes

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Regulation of gene expression using the RNA interference (RNAi) technology is a promising therapeutical approach with real perspective for clinical translation.Several clinical trials are already in course but none of them was proved to tackle brain diseases yet.In our laboratory, we have developed an RNAi against the mRNA of the tyrosine kinase fyn aimed to reduce the levodopa induced dyskinesia in Parkinson's disease.Combined with lentiviral delivered into the striatum, we have reduced dyskinesia in experimental mice (see M. Bordone oral presentation).Although the viral transduction was restricted only to the injected areas,fyn expression is ubiquitous throughout the brain and then we envisage to develop further precision of silencing among neuronal subtypes.We expect to make a molecular scalpel to provide a fine therapeutic option that will reduce side effects.To reach this goal we have designed a strategy using a modified Cre-LoxP system to restrict expression of RNA molecules into dopamine D1R-expressing neurons.We have cloned the synapsin promoter inverted between lox71/lox66 sequences upstream the EGFP reporter sequence.Then, the expression of EGFP will occur only in the presence of the recombinase Cre.In this poster we will discuss our strategy and show the first trials in vitro and in vivo to evaluate the correct functioning of the system.If recombination works with the reporter,the RNAi against fyn will be cloned instead of EGFP and will be tested in dyskinetic mice

Cellular and Molecular Neurobiology

P42.-Basal repression of BDNF in old neurons is triggered by CDYL-HDAC2 accumulation and SPHK2 decrease

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Over the past decade, accumulated evidence has indicated that one of the most dramatic changes that occur at the molecular level in the aging brain is the alteration of epigenetic mechanisms controlling gene expression. These mechanisms regulate a plethora of brain functions including activity-dependent transcription of memory genes and synaptic plasticity. BDNF is a critical factor required for learning and memory formation. In previous works, we described that the levels of BDNF mRNAs are significantly reduced in the hippocampus of old mice compared to young adults. This is because reduced cholesterol levels at the plasma membrane of old neurons impair proper NMDA receptor activity and downstream CaMKII signaling, favoring the formation of a repressive chromatin structure at BDNF promoters. Our recent data show that aging leads to the nuclear accumulation of the transcriptional repressor Chromodomain Y Like protein CDYL. In developing and in young neurons, neural activity triggers CDYL degradation to unleash its inhibition on target genes. However, in old neurons, the altered membrane composition consequence of cholesterol loss impairs CDYL degradation. Our results also show that CDYL repression is exerted by the recruitment of other repressor proteins such as HDAC2. In addition, reduced expression of Sphingosine Kinase 2, a protein involved in HDAC2 inhibition, further contributes to decreasing BDNF expression in the old.

Cellular and Molecular Neurobiology

P43.-Modulation of Tau 3R:4R Isoforms Imbalance Precludes Motor Impairments in a Mouse Model of Tauopathy

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The microtubule associated protein tau is involved in microtubule dynamics and axonal transport. Alternative splicing of exon 10 (E10) in the primary transcript produces tau protein isoforms with 3 or 4 microtubule binding domains (3R and 4R). The human normal adult brain bears equal amounts of both isoforms, while imbalances in 3R:4R relative contents are associated with several tauopathies, such as progressive supranuclear palsy (PSP). This condition leads to motor impairments as the most frequent etiology of atypical parkinsonism. In this study we analyzed motor phenotypes in the htau mouse model of tauopathy, which produces abnormal content of human 3R:4R tau isoforms. These mice show severe impairments in motor coordination which suggests that the 3R>4R abnormal levels could underlie the observed phenotype. We used a lentiviral mediated trans-splicing RNA reprogramming strategy to control the inclusion of E10 of the endogenous tau transcript in the striatum of the htau mice. Effective rescue of tau isoforms imbalance was observed at the protein level by Western Blot. The trans-splicing treatment precluded motor deficits in senile htau mice. Moreover, local modulation of isoforms imbalance improved neuronal firing of striatal neurons.

Our results suggest that motor coordination impairments observed in htau mice are related to the abnormal 3R:4R tau isoforms content, rising this model as a suitable tool to evaluate therapeutic approaches for tauopathies, including PSP.

Cellular and Molecular Neurobiology

P44.-Calcium signaling stimulates PERK pathway

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The endoplasmic reticulum (ER) plays a critical role in a variety of processes, where Ca2+ acts as a key messenger. It is well know that the accumulation of unfolded proteins into the organelle activates a signal transduction cascade called Unfolded Protein Response (UPR). The immediate response, which attempts to restore homeostasis, is the attenuation of protein synthesis due to the phosphorylation of eIF2α, by activation of PERK, a ER transmembrane kinase. We demonstrated that Calcineurin (CN) directly interacts with PERK increasing its activation. Also, we observed in astrocytes that the isoform β of CN (CNAβ-B) has a cytoprotective effect dependent on PERK. In addition, we detected Ca2+ ER efflux increase through the translocon during acute phase of UPR. Although the involvement of Ca2+ signaling in a multitude of cellular pathways has been well documented, little is known about its role in restoring homeostasis, once UPR is activated. Here, we evaluated the dependence of Ca2+ on PERK and eIF2α phosphorylation by immunoprecipitations, Western Blots and immunocitochemestry. Also was analyzed PERK/CNAβ-B interaction, after induces stress and pharmacologically modify translocon activity. The effect of ER Ca2+ efflux on PERK activation was further studied using a cell line knock-out for the 3 isoforms of the IP3 receptor. Overall these data strongly suggest that PERK is activated by Ca2+ signal originated through the translocon during acute phase of ER stress.

Cellular and Molecular Neurobiology

P45.-Dyrk1a overexpression induces APP axonal transport impairments in human neurons

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Neurons are highly polarized cells which rely on axonal transport of proteins and organelles to support synapse function. Kinases can regulate axonal transport by modulating cytoskeletal stability, activity of motor proteins and cargo loading into axons. Triplications of chromosome 21 in Down syndrome includes the DYRK1A (dual specificity regulated kinase 1A) gene, linked to the increase of Alzheimer's disease pathology. It was shown that DYRK1A can phosphorylate β-tubulin, APP and tau; suggesting a relevant role for DYRK1A in axonal transport regulation. To study whether DYRK1A modulates the transport properties of APP vesicles we generated human neurons derived from iPSC. Plasmids and viral vectors driving DYRK1A and DYRK1A-mCherry were generated to determine the effect of DYRK1A overexpression. Moreover, segmental velocities, run lengths, pauses, and reversions were computed using MATLAB algorithms. Using live-cell imaging of fluorescent APP vesicles we revealed that short term overexpression of DYRK1A impaired axonal transport by increasing the anterograde APP average velocity, without affecting retrograde movement. The proportions of anterograde, retrograde and stationary vesicles were similar to control suggesting that DYRK1A does not modulate vesicle loading but change motor-dependent transport properties. These findings suggest that DYRK1A regulates axonal transport and specifically APP dynamics, shedding light on a novel therapeutic target in neurodegeneration.

Cellular and Molecular Neurobiology

P46.-Protein malnutrition and premature aging: impact on cognitive skills and cellular senescence

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Early-life adversity, like protein malnutrition, increases the vulnerability to develop long-term effects on brain structures and function. The aim of this work is to study if perinatal protein malnutrition (PM) predisposes the occurrence of premature aging in a murine model and the mechanisms involved. Mice dams were fed with normal (NP, casein 20%) or low protein diet (LP, casein 8%) during gestation and lactation. Female offpring were evaluated at the ages of 2, 7 and 12 month. LP mice show a lower increase of weight along life and a tendency in having a lower mobility test at old age. We evaluated spatial memory and found that PM impairs this memory since they are young. Also, functionality of the olfactory system is lost earlier life in LP mice. We found a higher SA b-gal activity at old age in LP mice in the hippocampus that coincide with a premature upregulation of p21 senescence marker. We also found alterations in hippocampal neurogenesis at an old age showing LP mice a more immature dentate gyrus. Moreover, we evaluated oxidative stress and found a higher basal level in LP hippocampus together with a downregulation tendency of Catalase expression at a young age. We also found an upregulation by PM and age of Sirt7 which is recruited to DNA double-strand breaks. Together, our results show that perinatal PM causes long-term impairment in cognitive and physical skills through an accelerated senescence phenotype and increased in the oxidative stress in the hippocampus.

Cellular and Molecular Neurobiology

P47.-Dynamic association of Rpt5 to cold-stable microtubules in glial cells

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The ubiquitin-proteasome system (UPS) is a key cellular complex devoted to proteostasis maintenance. Alterations of its proteolytic activity are closely linked to pathogenesis of cancer or neurodegenerative disorders. Two main complexes form the 26S proteasome, the regulatory particle 19S proteasome and the central particle 20S proteasome. Different reports showed the impairment of proteasomal activity induced by stress conditions. Our study was aimed to analyze how are affected the UPS in glial cells exposed to cold temperature. As expected, a strong reduction on 20S proteasome activity was determined by enzymatic assay that, together with increased accumulation of poly-ubiquitinated proteins shown by Western blot, indicates a reduction in the activity of the UPS under cold condition. By immunofluorescence we observed a clear redistribution of Rpt5 (subunit of 19S complex) associated to a subpopulation of cold stable microtubules (Mts) but, no apparent changes on cellular distribution of □1-7 subunits of 20S was observed in Schwann cells, astrocytes or oligodendrocytes exposed to cold temperature. Biochemical evidences of Rpt5/MAP6/tubulin interactions were obtained from immunoprecipitation assays. We also found that this association of Rpt5 to Mts is reversible and specific of this subunit. Hence, the association of Rpt5 to Mts may correspond to a physiological response to cold temperature, as part of a reduced function of proteasome regulatory particle in glia cells.

Cellular and Molecular Neurobiology

P48.-Identification of calcium binding sites and structural determinants that regulate potentiation of α9α10 nicotinic cholinergic receptors.

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Nicotinic cholinergic receptors (nAChR) are pentameric cation-permeable ion channels activated by acetylcholine (ACh). Each nAChR subunit comprises a large extracellular amino-terminal domain, four transmembrane domains (TM1-TM4) and a long cytoplasmic loop between TM3 and TM4. The α9α10 nAChR mediates the inhibitory synapse between efferent fibers and outer hair cells of the cochlea. Expression of rat α9 and α10 nAChR subunits in Xenopus laevis oocytes yields functional α9 and α9α10 receptors, but not α10 homomeric nAChRs. One of the functional differences between α9 and α9α10 nAChRs is the modulation of their ACh-evoked responses by extracellular calcium (Ca2+). While α9 nAChRs responses are blocked by Ca2+, ACh-evoked currents through α9α10n AChRs are potentiated by Ca2+ in the micromolar range and blocked at millimolar concentrations. In order to identify the structural determinants responsible for these differences, we generated chimeric and mutant subunits, expressed them in Xenopus oocytes and performed electrophysiological recordings under two electrode voltage clamp. Our results suggest that the TM2-TM3 loop of the α10 subunit contains structural determinants responsible for the potentiation of the α9α10 nAChR by extracellular Ca2+. Moreover we identified α10 E45 and E175 as key residues of two potential Ca2+ binding sites involved in this potentiation.

Cellular and Molecular Neurobiology

P49.-Insulin resistance augments nicotinic acetylcholine receptor (nAChR) internalization and inhibits its cell-surface expression upon acute insulin treatment.

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The levels of nAChR in the plasma membrane (PM) depends on trafficking processes that involve the actin cytoskeleton (AC). In addition, the AC is required for the insulin stimulation of glucose uptake. Here we assess whether exposure to a sustained hyperinsulinemia-like milieu mimicking insulin resistance (IR) affects the stability of the nAChR in the PM. For this, CHO-K1/A5 cells, a clonal cell line heterologously expressing adult-type muscle nAChR, were incubated with 10nM insulin for 19-22h (long insulin) to develop IR. Effects of insulin on nAChR PM levels, ligand-mediated internalization (which depends on AC integrity), and actin filament (AF) morphology were assessed using specific fluorescence probes and immunofluorescence microscopy. IR was made apparent after long insulin by the lack of insulin responsiveness to glucose uptake. Acute insulin application (10, 25 and 100nM) produced a significant and dose-dependent increase of nAChR levels in the PM, already evident at 30min and more pronounced at 60min. These effects were accompanied by an increase in the number of AFs. When cells were subjected to IR, the acute effect of insulin on nAChR PM levels was abolished and a concomitant decrease of AFs was observed, together with a significant increase in ligand-mediated nAChR

internalization. In conclusion, insulin can affect the levels of expression of the nAChR in the plasmalemma and IR disrupts the endocytic dynamics of this receptor, possibly by altering the AC status.

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P50.-Quantitative expansion microscopy and its validation characterizing the spectrin membrane-associated periodic skeleton in axons

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Different fluorescent nanoscopy approaches have been used to characterize a 1-D periodic organization of actin, spectrin and associated proteins in neuronal axons and dendrites. This membrane-associated periodic skeleton (MPS) has been found in processes from all neuronal types examined across animals, suggesting that the structure is a conserved and fundamental component of these processes. The nanoscale architecture of the arrangement (periods of ~190nm) lays bellow the resolution limit of conventional fluorescent microscopy. This finding has led to a small number of articles and we believe it is because nanoscopy requires special analyzes and expensive equipment. In this report, we aimed at solving this isuue by using protein-retention expansion microscopy (ExM) to evidence the MPS of axons. We first explored means to estimate expansion factors for protein structures within the cell. We then describe the protocol that produces an expanded specimen that can be examined with any conventional fluorescent microscopy (confocal, epifluorescence o spinning disk) that allows quantitative nanoscale characterization of the MPS. We validate our characterization by showing that the resolved details using prot-ExM rivals those obtained with commercially available stimulated emission depletion microscope (STED). We conclude that ExM allows for three-dimentional, multicolor and quantitative characterization of the MPS using accesible reagents and conventional fluorescent microscopes.

Cellular and Molecular Neurobiology

P51.-Antiamylod compounds designed for inhibition of αS aggregation

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Alpha-synuclein (aS) aggregation is linked to the development of Parkinson's disease. The use of aggregation inhibitors as molecular probes of the structural and toxic mechanisms related to amyloid formation is an active area of research. In this study we applied different biophysical tools to investigate the binding and anti-amyloid properties of the small molecule PfTS-3 on the amyloid fibril assembly of the protein S; as well as comparing it with the previously studied antiamyloid agent Phthalocyanine tetrasulfonate (PcTS). These compounds bind to

the monomeric form of the S, where the N-terminal region of the protein represents the binding interface. Although aromatic and electrostatic interactions are involved in complex-formation, more specific interactions were described for the PcTS molecule. Interestingly, both interactions leads to inhibition of S assembly. The molecular mechanisms and structural basis behind these inhibitory interactions are well different and will be matter of our discussion.1

1. Valiente-Gabioud AA, Miotto MC, Chesta ME, Lombardo V, Binolfi A, Fernández CO. Phthalocyanines as Molecular Scaffolds to Block Disease-Associated Protein Aggregation. Acc Chem Res. 2016;49(5):801-808.

Cellular and Molecular Neurobiology

P52.-Changes in pre and post synaptic proteins during LTM early consolidation

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Memory consolidation requires protein synthesis and degradation. In this way, it was described that postsynaptic receptors change its expression after memory acquisition or plasticity induction:NMDAR expression rise 70 minutes and decrease, to control levels, 90 minutes after training, while AMPAR expression is increased long after 90 minutes. On the other hand, NMDAR and AMPAR are associated to scaffold proteins that help to assemble the postsynaptic density (PSD) and are called MAGUKs (membrane-associated guanylate kinases). These MAGUKs are: PSD93, PSD95, PSD97 and SAP102. GluN2A, a NMDAR regulatory subunit is directly associated to PSD95. Furthermore, this last controls AMPAR number at PSD. In this work, we investigate changes in pre and postsynaptic sides, using a presynaptic (Synapsin1, Syn) and a postsynaptic marker (PSD95) 70 minutes after memory acquisition, at same time that NMDAR subunits rise.For this reason, we trained adult Wistar rat in an Inhibitory Avoidance paradigm (IA) and, immediately or 70 minutes after training, we dissected both hippocampi and analyze PSD95 and Syn1 expression by western blot, in total homogenates and also, in PSDs fractions. We found that Syn1 levels were increased in membrane fractions while PSD95 did not change it expression in both total and PSDs homogenates. These results could suggest that changes in pre and postsynaptic sides have different dynamics that we will investigate in a near future.

Cellular and Molecular Neurobiology

P53.-REST as a possible mediator of the neuroprotective effect of extra virgin olive oil

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REST (Repressor Element 1-Silencing Transcription factor) is a modulator of neuronal genic expression that acts during aging in healthy human and murine's brain, conferring oxidative stress resistance and protection against toxic insults associated with Alzheimer Disease (AD), however their levels are diminished in patients and murine models of AD. On the other hand, extra virgin olive oil (EVOO) has antioxidants properties being the main dietary component of Mediterranean populations, and several studies have correlated its consumption with the normal cognitive abilities in the Mediterranean elders. We study the neuroprotective effect of EVOO and their relationship with REST in frontal cortex of 18 months old transgenic rat (Tg), type AD cognitive impairment

model (hemyzigous McGill-R-Thy1-APP) and their non-transgenic (NoTg) littermates. Rats were fed ad-libitum, and supplemented with 900mg/kg.day EVOO (4 cal/kg.day) or corn oil (CO, 4 cal/kg.day) as placebo, for 6 months. We found a significant increase in cognitive performance (novel object recognition test) and REST levels of Tg-EVOO vs Tg-CO rats, while there were no significant differences between Tg-EVOO and controls groups (NoTg-EVOO and NoTg-CO; ANOVA, Tukey post-test, $p<0.05$). Together these results suggest that REST is involved in neuroprotective effect of EVOO in our transgenic model of cognitive impairment. In complementary studies, genes regulated by REST that confer neuroprotection are being evaluated.

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P54.-Participation of TGFβ on the remyelination process

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Our previous results have demonstrated the interplay between Notch and TGFβ signaling pathways in adult neural progenitor cells (NPC) cultures from subventricular zone (SVZ). In these cultures, TGFβ favored oligodendroglial cell fate and oligodendroglial precursor cell (OPC) proliferation, and induced OPC differentiation into mature OL. Considering the possible participation of TGFβ in the repair mechanisms during demyelination, the aim of the present work is to study, both in vitro and in vivo, the changes induced by this cytokine on the OPC maturation and on the inflammatory process. To analyze TGFβ effect on OPC maturation, in vitro experiments were carried out on OPC primary cultures obtained from newborn rat cerebral cortex. After OPCs treatment with TGFβ for 3 days, no changes in the percentage of PDGFRα+ and MBP+ cells were observed compared to control. However, the presence of TGFβ induced an increase in the morphological complexity of OPC and mature OL. For in vivo experiments control and 14-day-CPZ-treated rats were intraperitoneally injected with TGFβ or its vehicle during 3 days before removing the toxic from the diet. Preliminary results obtained from corpus callosum immunohistochemistry analyses showed a slight increase in MAG+ cells concomitantly with a decrease in Iba1/CD68+ cells in CPZ-treated animals. These results suggest that TGFβ might contribute to OPC differentiation during demyelination and reduce the inflammation associated to demyelination.

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P55.-CaMKII delta regulation in memory maintenance and persistence

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Genetic expression regulation is considered a key step in long term memory formation. Recently, we have found that NF-kB promotes the expression of a gene that codes for the calcium-calmodulin-dependent type 2 protein kinase delta isoform (CaMKII delta), specifically in memories that lasts over 7 days.Subsequently, we found evidence that its blockage during consolidation by an antisense DNA affects the persistence of object recognition memory. In this work we decided to study CaMKII delta gene expression, its epigenetic regulation and the need for such expression in memory maintenance and persistence of object recognition task in mice. Our hypothesis is that this gene and its protein play a key role in these processes. For this purpose, we first study

the temporal expression of CaMKIId mARN after a strong training. The training we used induces a memory that lasts for at least 7 days. 48 hs after training, we observed in hippocampus from trained mice a significant increase in CaMKIId mRNA compared to habituated animals.These results suggest, as our previous results, that this gene expression is maintained as long as memory retention lasts.

Cellular and Molecular Neurobiology

P56.-Perinatal protein malnutrition-induced anhedonia is associated to a reduced hippocampal dendritic spine density and BDNF levels in the adult offspring

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Growing evidence indicates that depression is closely related to neuronal morphological alterations in specific brain areas. In addition, brain derived neurotrophic factor (BDNF) plays a key role in the structural plasticity induced by such disorder. In order to investigate neurobiological substrates linked with early protein undernutrition-facilitated depressive-like behaviours, we studied the impact of nutritional insult on the dendritic spine density at CA1 hippocampal neurons and BDNF levels in this brain area. Thus, adult animals submitted to a perinatal protein deprivation schedule (D-rats) and well-nourished animals (C-rats) were exposed to the sucrose preference test, a paradigm usually employed to evaluate anhedonia. After the test, different groups of C- and D-rats were perfused for dendritic spine analysis or sacrificed for BDNF levels quantification. According to previous results, D-rats showed a significant reduction of sucrose preference compared to C-rats. Furthermore, D-animals elicited a lower density of total dendritic spines, particularly mature ones, which was correlated with decreased levels of BDNF in the hippocampus. These results suggest that morphological and molecular alterations in the hippocampus of malnourished animals may contribute to a lower ability to cope with appetitive stimuli.

Cellular and Molecular Neurobiology

P57.-hiPSC- and hNPC-derived Extracellular Vesicles: composition and biological activity

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Extracellular vesicles (EV) are nanovesicles (50-200 nm) released to the extracellular microenvironment by most cell types. EV regulate biological processes by transferring lipids, proteins and miRNA cargo between cells during physiological and pathological conditions. Given their ability to transfer bioactive components and their biocompatibility, EV are increasingly being explored as potential therapeutic agents. Stem cell-derived EV promote endogenous regenerative mechanisms and functional recovery in animal models of the central nervous system (CNS). Whether EV secreted by human induced pluripotent stem cells (hiPSC) and human neural precursor cells (hNPC) might have similar therapeutic potential in CNS diseases is still unknown. Moreover, the

molecular and cellular mechanisms responsible for their potential regenerative and immunomodulatory effects are unclear. Here, we used a combination of in silico systems biology, biochemical and optical approaches to evaluate compositional and morphological differences between EV secreted by hNPC and hiPSC. These results will help us to shed some light on how stem cell-derived EV might exert their regenerative effects and improve their therapeutic potential in CNS disorders.

Cellular and Molecular Neurobiology

P58.-Rejuvenating the brain with chronic exercise through adult neurogenesis

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The aging brain presents a general decline in plasticity that also affects hippocampal neurogenesis. Besides the well-known reduction in the rate of neuronal generation, development of new neurons is largely delayed in the aging brain. We have recently shown that this slow development is accelerated when middle-aged mice perform voluntary exercise in a running wheel. It is unclear whether the effects of exercise on neurogenic plasticity are persistent in time in a manner that might influence neuronal cohorts generated over an extended time span. To clarify these issues, we examined the effects of exercise length in three-week-old neurons and found that their development is accelerated only when running occurs for long (3–4 weeks) but not short periods (one week). Furthermore, chronic running acted with similar efficiency on neurons that were born at the onset, within, or at the end of the exercise period, lasting until 3 months. Interestingly, no effects were observed on neurons born one month after exercise had ended. Our results indicate that multiple neuronal cohorts born throughout the exercise span integrate very rapidly in the aging brain, such that the effects of running will accumulate and expand network assembly promoted by neurogenesis. These networks are likely to be more complex than those assembled in a sedentary mouse due to the faster and more efficient integration of new neurons.

Cellular and Molecular Neurobiology

P59.-Tau and APP relation in human cerebral organoids with the Swedish mutation

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Alzheimer disease (AD) is the main neurodegenerative ailment affecting human populations (1,2). Mutations in amyloid precursor protein (APP), which give rise to amyloid-beta (Aβ) when processed, are linked to familial AD. The Swedish (Swe) mutation occurs next to the Aβ region and increases amyloidogenic processing (3). Tau is a microtubule associated protein that belongs to the MAP2 family, it is involved in axonal transport and neurite growth (4). In AD tau is hyper-phosphorylated and aggregated, forming neurofibrillary tangles (5). Alternative splicing produces several tau isoforms, some of which (3R and 4R) are linked to the onset of dementia (6). Until this day the idea of studying tau modifications related to the Swe mutation in a model with human genomics and proteomics has not been fulfilled. We produced human cerebral organoids from induced pluripotent stem cell (IPSC) colonies obtained from a control patient and a patient with the Swe mutation (7). Fully grown and

differentiated organoids were processed for further analysis. Using Congo red staining and Aβ, we observed amyloid aggregates in samples with the Swe mutation. Using specific antibodies we observed changes in tau levels in Swe and control organoids as wells as a distinct tau 3R/4R isoform localization in control and Swe samples. All in all, using a human cerebral model, we describe the AD pathology in Swe samples as well as a particular expression of tau isoforms in Swe and control organoids.

Cellular and Molecular Neurobiology

P60.-Impact of the human Val66Met polymorphism of the bdnf gene on the structure and function of dopaminergic neurons

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A SNP in the BDNF gene is present in more than 25% of the human population. It results in a valine for methionine substitution at position 66 (Va66Met) within the BDNF prodomain (pBDNF) sequence. This SNP is associated with increased susceptibility to develop certain psychiatric and neurodegenerative disorders that involve dopaminergic neurons, such as anxiety and Parkinson's disease. First we showed that pBDNF and its receptor complex of SorCS2 and p75NTR is expressed in the CNS dopaminergic systems. Then, we studied the actions of the Met prodomain on primary dopaminergic neurons and in the major dopaminergic systems in vivo. Interestingly, we found that dopaminergic neuron cultured from BDNFMet/Met knock-in mice displayed shorter processes as compared to BDNFVal/Val animals. Moreover, we studied in vivo if the presence of the Met allele increases the susceptibility of dopaminergic neurons to degenerate after the injection of the specific neurotoxin 6-OHDA. We detected that the nigrostriatal dopaminergic system of BDNFVal/Val and BDNFMet/Met mice are equally susceptible to 6-OHDA (TH immunodetection and motor behavioral tests). However, we found that the degeneration of dopaminergic neurons increases anxiety-related behaviors only in the BDNFMet/Met mice. Thus, we hypothesized that other CNS dopaminergic systems are more susceptible to degenerate in the Met allele carriers which could explain the increased incidence of psychiatric disorders associated with the Val66Met SNP.

Cellular and Molecular Neurobiology

P61.-In silico characterization and functional analysis of non-synonymous polymorphisms (nsSNPs) present in GPM6A's extracellular coding regions

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Neuronal membrane glycoprotein M6a promotes neurite and axonal outgrowth, filopodia/spines formation and synaptogenesis in neuronal cultures. Altered expression or single nucleotide polymorphisms (SNPs) in GPM6A are associated with neurological disorders such as schizophrenia, depression, claustrophobia and Alzheimer's disease. However, the molecular mechanisms underlying the development of such pathologies remain unknown. M6a shares topology with the tetraspanin family, containing: four transmembrane domains, two extracellular loops (EC1 and EC2), an intracellular loop and the N- and C-regions facing the cell cytoplasm. Interestingly, tetraspanin's extracellular loops are crucial for specific and functional protein-protein interactions.

Accordingly, we speculate that certain amino acids within M6a's extracellular loops mediate specific interactions thus contributing to its function. We selected 13 non-synonymous SNPs located at GPM6A extracellular regions from the dbSNP database. In silico analysis predicted that all nsSNPs decrease protein stability and/or have potential functional effect. Indeed, functional analysis showed that one SNP located in EC1 (T71P) and four in EC2 (M154V, F156Y, R163Q and T210N) impaired M6a-induced neurite extension and/or filopodia in neurons. In conclusion, we provide evidence of the critical role of certain residues located on EC1 and EC2 on M6a function and the potential risk of these nsSNPs.

Cellular and Molecular Neurobiology

P62.-Isolation of brain synaptosomes with functional mitochondria

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Mitochondrial function in nerve terminals is essential to maintain adequate neuronal function. The analysis of bioenergetics at synapses is relevant for the study of mitochondrial alterations in neuronal diseases. Hence, we propose a method for brain synaptosomes isolation with functional mitochondria. Mouse brain cortexes from two mice were homogenized and centrifuged at 1000 g for 10 min. The supernatant was layered on a gradient of 3, 8 and 13% Ficoll and centrifuged at 40000 g for 11 min. Mitochondrial function and synaptosomes structural and functional properties were analyzed in the synaptosomal fraction. The presence of intact synaptosomes was detected by flow cytometry after immunostaining with SNAP-25/FITC. Enzymatic activity of acetylcholinesterase and mitochondrial complexes I-III and II-III was measured both in synaptosomal fractions and in total homogenates. Data showed a 1.2-1.4-fold enrichment of acetylcholinesterase and mitochondrial respiratory complexes enzymes relative to the initial homogenate. Oxygen consumption was determined in synaptosomes showing a basal respiration of 11 ± 1 ng at O/min.mg protein, which responded to the addition of oligomycin (5.1 ± 0.4) and FCCP (14.9 ± 0.5). The use of TMRE by flow cytometry indicated a detectable mitochondrial membrane potential which decreased 90% after addition of FCCP. We conclude that the present isolation protocol constitutes an easy and fast method to obtain synaptosomes containing functional mitochondria.

Cellular and Molecular Neurobiology

P63.-Neuroprotective Insulin-like Growth Factor 1 (IGF1) gene therapy for a rat model of sporadic Alzheimer's disease

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Sporadic Alzheimer's disease (SAD) is a progressive neurodegenerative disorder with no cure. We are interested in developing therapeutic strategies to overcome SAD-neurodegeneration. To this end, we implemented gene therapy (GT) for IGF1 in a rat SAD model induced by intracerebroventricular injection of streptozotocin (icv-STZ). Animals were divided into 3 experimental groups: Sham, STZ and STZ+IGF1. STZ and STZ+IGF1 groups received 3 mg/kg STZ-icv. Seven days later, the STZ+IGF1 group received icv an adenoviral vector expressing recombinant IGF1. During the last two weeks until the end of the study (day 24 post-icv-STZ), we performed several behavioral tests. Additionally, we performed in the hippocampus inmunohistochemistry to analyze neurogenesis and microglial cells, and Western Blots to assess the levels of proteins involved in the IGF1 signaling pathway. Our results show that IGF1-GT improved marble-burying behavior, hippocampus-dependent spatial memory, object recognition memory and decreased depression-like behavior, all features affected by STZ. Also, brain IGF1 overexpression restored neurogenesis in the STZ animals and modulated the microglial population. Importantly, the assessment of phosphorylated proteins levels revealed that IGF1 therapy effect was mediated by triggering IGF1 receptor signaling pathway. We conclude that IGF1 over-expression has an interesting potential for the treatment of SAD.

Cellular and Molecular Neurobiology

P64.-Glyphosate exposure impairs nervous system development and functioning

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The proper formation, maintenance, and elimination of synapses are crucial to guarantee the formation of a functional nervous system. During development, these processes become particularly vulnerable to environmental contaminants. Glyphosate (Glyph) is one of the most used agrochemical around the world and from the late 1970s to 2019 there was a 100-fold increase in the frequency and volume of application. Therefore, in this work, we studied the effect of Glyph on synaptic function during development through in vivo and in vitro assays. Firstly, we evaluated the expression of synaptic proteins in the hippocampus of Glyph-treated rats and in hippocampal cultured neurons exposed to Glyph during a critical period of synaptogenesis. Surprisingly, both in vivo and in vitro assays evidenced a significant decrease in PSD-95 and Synapsin I, two well-known synaptic markers. Additionally, to further analyse the effect of Glyph on synaptic plasticity we used mature hippocampal cultured neuron. Results showed that the exposure to Glyph impairs dendritic spine density and morphology. Finally, we evaluated spatial learning and memory by the Morris water maze test and we found cognitive dysfunction in Glyph-exposed rats compared to controls. In conclusions, these findings suggest that Glyph exposure affects the normal development of nervous system impairing synaptogenesis and neuronal connectivity.

Cellular and Molecular Neurobiology

P65.-Dam Early Free Access to Hypertonic NaCl Solution Induces a Long-Term Effect on Offspring Basal Chronic Brain Cell Activity

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Exposure to hyperosmotic environment during a pre/postnatal period can differentially program the fluid intake and excretion pattern in a way that persists until adulthood. Our results suggest that maternal voluntary ingestion of hypertonic NaCl solution during pregnancy and lactation until one week post-weaning (MP-Na) alters the offspring's central osmoregulatory mechanisms. Our aim was to evaluate the impact of MP-Na on the basal expression of TRPV1 osmosensitive channel (by western blot) and chronic neuronal activity along the brain osmosensor areas of adult's offspring by the immunohistochemical detection of brain Fra like protein (Fra-LI), alone or combined with vasopressin (AVP). The imprinting animals (MP-Na group) showed increased Fra-Li immunoreactivity(ir) in the organum vasculosum of the lamina terminalis (OVLT)($p=0.018$) but not in the subfornical organ. Fra-AVP-ir neurons along the supraoptic nucleus(SON) and in the lateral magnocelular subdivision of the paraventricular nucleus (PaLM) show a significant decreased and increased respectively in MP-Na animals(SON $p=0.03$ and PaLM $p=0.02$).The expression of TRPV1 in OVLT and SON were not significantly different after MP. Taking into account our previous evidence, these results indicate that the availability of a rich source of NaCl during the perinatal period induces a long-term effect on drinking and the basal neural activity along the OVLT, SON and PVN nuclei implicated in the control of hydroelectrolyte balance.

Cellular and Molecular Neurobiology

P66.-Intrinsic blue-light responses in avian Müller glial cells involve non-visual opsin activation and calcium release from internal stores

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The retina of birds contains different types of photoreceptors cells: the visual photoreceptor cells (cones and rods), the Opn4-expressing cells (ganglion and horizontal cells), and the Müller glial cells (MCs) that express the nonvisual opsins Opn3 and Opn5 (blue and UV-light sensitive). MCs are the main glial cell type in vertebrates' retina located all along the inner retina and controlling its physiology by debris phagocytosis, K+ uptake, and trophic factors and neurotransmitters release. The present work aims to further characterize the intrinsic photoreceptor capacity of the inner retina focusing on MCs. Therefore, Ca+2 responses to blue light (BL) were evaluated by fluorescence Ca+2 microscopy in enriched MCs primary cultures. A MCs subpopulation (45%) responded to a BL pulse (20 sec) by increasing intracellular Ca2+ levels up to 20%. This response was not observed in presence of the retinal bleacher hydroxylamine nor with red light stimulation. Further testing was performed with the Ca+2 chelator EGTA and the inhibitors for SERCA (thapsigargin), IP3 receptors (2-APB), and G protein-coupled receptors (Suramin). In this conditions, BL responses were absent except for EGTA treatment. Our results show a direct and specific photic response of MCs to BL stimulation involving opsin and G protein activation that promote Ca+2 release from internal stores; thus suggesting new roles for MCs in retinal physiology, possibly in visual and nonvisual processes regulated by light.

Cellular and Molecular Neurobiology

P67.-Role of RhoD GTPase in neuronal development and neuronal polarity

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Neurons are highly polarized cells typically extending a long thin axon and multiple short branched dendrites. These specialized compartments are developed through the coordination of cellular and molecular mechanisms in order to ensure the proper functioning of the nervous system, and are highly regulated by several small Rho GTPases with their effectors controlling different aspects of neuronal morphology. Among others, these events include actin and microtubules cytoskeleton assembly, and the addition of membrane in neuron specialized regions. Even though most of studies have been focused on classical Rho GTPases (RhoA, Rac1 and Cdc42), other less studied members of this family such as RhoD suggest to have unique effects on cytoskeleton and membrane dynamics. In this study we have analyzed the role of RhoD during the development of axonal polarization and neurite extension. We have also designed and characterized an unimolecular activity RhoD biosensor based on resonance energy transfer (FRET) in order to study the space-time dynamics of this Rho GTPase in fibroblast and neuron cells. Finally, we have evaluated how RhoD affects different dynamic parameters of microtubules cytoskeleton.

Cellular and Molecular Neurobiology

P68.-Passive immunization with anti-Myelin-associated glycoprotein antibodies induces an autistic phenotype associated with altered postnatal neurodevelopment

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High titer of anti-Myelin-associated glycoprotein antibodies (anti-MAG mAb) has been observed in infants with autism spectrum disorders (ASDs). We analyzed the possible contribution of MAG to the pathogenesis of ASD by passive immunization with a function-blocking anti-MAG mAb in wild type mice at perinatal stages. Anti-MAG mAb treatment was associated with development of an autistic phenotype characterized by alterations of social interaction and social recognition behaviors, reduced ultrasonic vocalizations and increased stereotyped behaviors with preservation of motor skills. Morphometric stereological analyses showed altered cerebellar neurodevelopment characterized by a transient increase in the number of granule cells at P7 in lobes VI/VII (but not at lobe X) followed by increased neurodegeneration at P14-21. Similarly, we observed a preferential increase of Purkinje cells number in lobes VI/VII characterized by a dystrophic morphology, although their number remained constant along the study. Morphometric studies also identified alterations in cell/size number in prefrontal cortex. MAG-null mice displayed behavioural and neurodevelopmental alterations closely resembling anti-MAG-treated mice. Our results show that blocking MAG function induces phenotypic behaviors and neurodevelopmental alterations associated with ASDs. Altogether, our data supports a pathogenic role of anti-MAG autoantibodies as a leading cause for the development of ASDs in a clinical subgroup.

Cellular and Molecular Neurobiology

P69.-Functional and structural characterization of human heteromeric 5-HT3 receptors

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5 HT3 receptors are the only serotonin (5-HT) receptors that belong to the Cys-loop receptor family. They mediate fast excitatory transmission in central and peripheral nervous system. Five different subunits (A-E) have been identified in humans. The A subunit is able to form homomeric receptors (5-HT3A), and it can combine with the B subunit to form heteromeric receptors. We here evaluated if the C-E subunits can combine with the A to form heteromeric receptors. To this end, we constructed a high-conductance A subunit (AHC) that allowed to obtain single-channel events. After expression of the AHC we observed events with an amplitude of ~4.7 pA corresponding to the 5 HT3AHC receptor. However, when AHC was expressed in combination with one of the C-E subunits, events with different amplitudes were detected, thus confirming the expression of heteromeric receptors. From macroscopic currents we observed an increase in the 5-HT EC50 value for each of the heteromeric receptors with respect to that for the 5 HT3AHC receptor. In-silico studies provided insights into the contribution of the different subunits to the 5-HT binding site. Our results demonstrate that C-E subunits can combine with the A subunit to form heteromeric receptors. These results bring structural and functional details about the different human 5-HT3 receptors and will contribute to the development of selective therapies targeting this receptor family.

Cellular and Molecular Neurobiology

P70.-In vivo effect of a single dose of mesenchymal stem cells exogenously expressing IGF-I in a spinal cord compression model

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An important aim in nervous system repair is to develop strategies that avoid main consequences of spinal cord injury by restricting tissue damage, neural death and locomotor function loss. In this regard, application of mesenchymal stem cells as vehicles of gene therapy could be a useful approach. In this study, a compression injury model was developed by applying an aneurysm clip to the spinal cord of BALB/c mice at the thoraco-lumbar level for 1 min. Mesenchymal stem cells, transduced with an adenovirus containing rat IGF-I (AdIGF-I-MSCs) or GFP (AdGFP-MSCs) gene sequences, were injected at the core of the affected zone 7 days post-injury. Locomotor behavioural and histological studies were performed. Locomotion was evaluated in an open field by applying the Basso Mouse locomotor scale rating and foot printing analysis. No apparent changes among experimental conditions were observed with regards glia cells in broad areas within the injury zone. Our preliminary data suggest an improvement in locomotion task and coordination walking pattern after AdIGF-I-MSCs application. This outcome might involve a modulation and/or plasticity of spinal circuits and locomotor neuronal networks.
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Cellular and Molecular Neurobiology

P71.-Role of actin cytoskeleton dynamics and its modulator Cofilin 1 in fear memory processing

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Synaptic efficacy modulation, in tight relationship with synaptic morphological changes, is proposed to underlie long-term memory processing. Such plasticity is known to occur in dendritic spines. These small actin-rich protrusions from dendrites provide a suitable biochemical compartment to locally control and integrate different inputs, due to spatial confinement. Therefore, spine number, morphology and underlying actin polymerization level can modulate synaptic efficacy in many different ways. Actin cytoskeleton has major regulating factors of its depolymerization such as Cofilin 1 (Cfl1), becoming an attractive target to study processes underlying dendritic plasticity. Using a contextual fear conditioning paradigm in mice, we found that pharmacological induction of depolymerization of actin filaments through the inhibition of LIM kinase, which is in turn an inhibitor Cfl1 activity, causes impairment in memory reconsolidation, as well as in memory consolidation. On top of that, Cfl1 activity is inhibited and its mRNA is downregulated in CA1 neuropil after re-exposure to the training context. Moreover, by pharmacological disruption of actin cytoskeleton dynamics, the process of memory extinction can either be facilitated or impaired.

Cellular and Molecular Neurobiology

P72.-EphA3 ectodomain and uPA increase retinal ganglion cells axon growth by regulating FAK activity

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The Eph/ephrin system regulates axon guidance during chicken retinotectal mapping. We demonstrated that tectal EphA3 stimulates axon growth of nasal retinal ganglion cells (RGC) toward the caudal tectum preventing them from branching in the rostral tectum. The complex formed by urokinase plasminogen activator (uPA) and its receptor (uPAR) promotes neuritogenesis and is closely related to the phosphorylation of the focal adhesion kinase (FAK). The purposes of this work were to study the relationship between the effects of EphA3 and uPA on RGC axon growth and which molecules participate downstream in these processes. We cultured chicken embryo dissociated retinal neurons and retinal explants exposed to control conditions, to EphA3 ectodomain (EphA3-Fc), to uPA or to EphA3-Fc plus uPA to evaluate their effects on axon growth and on FAK activity. The results showed that: uPA produces a higher increase in axon growth than the EphA3-Fc and that the combination of both of them produces an intermediate effect. Besides uPA and EphA3-Fc modify FAK activity in a different way. This shows that uPA and EphA3 increase RGC axon growth in a non-additive way and that both of them regulate FAK activity.

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Cellular and Molecular Neurobiology

P73.-Hyaluronic acid depletion effects on neurosphere cultures

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Hyaluronic acid (HA) is a linear non-sulfated glycosaminoglycan found in the extracellular matrix that acts as structural support and exerts regulatory functions in several tissues. In the brain, HA is critical for the maintenance of subventicular zone (SVZ) architecture and acts as a neural stem cell and progenitor cell (NSC/NPC) niche during CNS development and regeneration. HA dysregulation has been previously associated to remyelination failure in animal models of demyelination. In the present work we isolated NSC/NPC from periventricular mouse brain tissue and cultured as neurospheres (NS) in order to study in vitro HA requirements for NSC/NPC biological functions. NS cultures were first characterized to confirm cell multipotency. We evaluated the effects of 4-Methylumbelliferone (4-MU), a coumarin derivative which inhibits HA synthesis, throughout NS culture progression. Floating NS were generated at all doses of 4-MU used. NS size significantly decreased at doses higher than 125µM 4-MU, suggesting that HA synthesis inhibition affects NSC/NPC proliferation and correlating with a significant decrease in 4-MU-treated culture metabolic activity. Adhered NS treated with 4-MU showed a reduced number of migratory cells and inhibition in the elongation of GFAP+ processes from the NS surface. These findings reinforce HA requirements for the control of NSC/NPC proliferation and migration and could help develop new strategies to improve CNS regeneration.

Cellular and Molecular Neurobiology

P74.-The effects of Wnt7b signalling on axonal morphology

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In the nervous system, Wnt secreted molecules play important roles in the formation of functional neuronal circuits by regulating axon pathfinding and remodeling, dendritic development and synapse assembly. Importantly, Wnt proteins regulate cytoskeletal network and the activity of different effectors to control neuronal polarity, axon and dendrite development and maturation. It has extensively been shown that Wnts directly regulate the dynamic and organization of microtubules. In this work, we evaluate the potential role of Wnt7b during earlier neuronal development, particularly on axonal growth. Our findings suggest that Wnt7b is specific involved in the establishment of neuronal polarity and in axonal outgrowth. To go further, we examined the intracellular signaling triggered by Wnt7b. Pharmacological inhibition of non canonical pathway reveals that inhibition JNK (PCP pathway) abolished the Wnt7b mediated axonal effects over axonal architecture. Consistently, we then evidenced the JNK activation by Wnt7b using western blot and immunofluorescence techniques. More analyses need to be performed in order to determine whether the cellular mechanism triggered by Wnt7b to modulate axonal morphology involves changes on JNK mediated-microtubule stability. To proceed further, we will evaluate the contribution of small Rho GTPases, as critical regulators of microtubule dynamic, on Wnt7b axonal effect.

Cellular and Molecular Neurobiology

P75.-Evidence for a differential dorso-ventral hippocampal sensitivity to chronic stress in female rats: Relevance to sex biases in mood disorders

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Depressive disorder is nearly twice as prevalent in women versus men. Anatomical and functional modifications are observed in the hippocampus of depressed patients, which may in part be induced by chronic stress (CS) in rodents. These modifications include changes in the subunit composition of AMPA and NMDA receptors mainly in the dorsal hippocampus of male; changes that correlate with the cognitive deficits observed in stressed rodents. In contrast, the ventral pole is a regulator of emotions whose dysfunction induces anxiety- and depressive-like behaviors in female rodents under CS. With these antecedents, we hypothesized that dorsal and ventral hippocampus show differences in their sensitivity to chronic stress and glucocorticoids administration in female rats; suggesting that these differences may account the sex-biased effect of stress on emotions and cognition. Here, we demonstrated by RT-qPCR and western blot that in adult Sprague-Dawley female rats, unlike males, CS (restraint, 2.5 h/day, 14 days) decreased both GluA1 and GluA2 AMPA receptor subunits and decreased NR2A/NR2B at the synaptic level in the ventral hippocampus, effect that is emulated by CORT administration (30 mg/kg/day for 14 days), which could be related to depressive-like behaviors. These results suggest that CS and glucocorticoids modifies the function of the ventral pole of the hippocampus in female rats, which could explain the phenotypic sex bias observed in depressive disorder.

Cellular and Molecular Neurobiology

P76.-Alpha-Synuclein-induced intracellular trafficking defects as a potential pathogenic mechanism for Parkinson's Disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons of the substantia nigra. One of the hypotheses regarding the molecular mechanisms involved in the development of this disease postulates that intracellular trafficking defects are initial events in the pathogenesis of this disorder. It is known that increased expression of α-synuclein (AS) is associated with a higher incidence of PD. However, the underlying cellular and molecular mechanisms have not yet been fully elucidated. In order to study whether AS is capable of affecting the dynamics of vesicular transport between the endoplasmic reticulum (ER) and the Golgi apparatus, and the release of vesicles from the latter towards neural processes, we utilized a state-of-the-art system based on fusion proteins that are retained in the ER and can be released synchronously to the Golgi apparatus and the rest of the secretory pathway. Interestingly, we found that α-synuclein expression induces a delay in the release of vesicles from the Golgi apparatus to the processes in rat hippocampal neurons. These results suggest that the toxicity of α-synuclein may be due, at least in part, to the

delay or blockage of the exocytic pathway. We are currently testing if the same effect is present in human reprogrammed neurons derived from induced pluripotent stem cells (iPSC).

Cellular and Molecular Neurobiology

P77.-Deletion of the arginyltransferase gene in oligodendrocytes impairs myelination

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Arginyltransferase (Ate1) adds an arginine residue to multiple protein substrates; whose post-translational modification modulate cellular processes such as migration, proliferation and neuronal growth; however, its role in Central Nervous System (CNS) is still uncertain. Oligodendrocyte precursor cells (OPCs) undergo morphological changes during differentiation into mature oligodendrocytes (OLs) in the CNS. The later generate the myelin that surrounds axons for rapid propagation of action potential. This study was aimed to elucidate the role of Ate1 through CNS myelination. Conditional deletion (cKO) of Ate1 from OLs with the Cnp-cre promoter resulted in differential changes on OL differentiation throughout CNS development. Analysis of OL populations in the corpus callosum (CC) shows that cKO mice at P14 have a reduced number of total (Sox10+) OLs respect control mice. Whereas at P21, Sox10 and mature OLs (CC1+) appear normal. Concomitantly at P21, increased proliferation of OPC and astrocytes populations was found in the CC of cKO mice. Nonetheless, a reduced number of CC1+ OLs was determined in the spinal cord of cKO, showing a delay in the maturation of OL between different CNS regions of Ate1 cKO mice. Hence, deletion of Ate1 in OLs induced an increase of local OPC proliferation together with astrogliosis response, which may compromise the myelin maintenance of adult mice. Future studies will address which proteins involved in OLs maturation are substrates of Ate1.

Cellular and Molecular Neurobiology

P78.-Roles of KIF5C on neuronal polarization and neocortical formation “in situ”

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Three early signals of asymmetry occur in a single neurite of neurons in culture at stage 2 of differentiation and are essential for polarization: i) Accumulation of stable microtubules; ii) Enrichment of the plasma membrane with activatable IGF-1r; and iii) Polarized transport of the microtubular motor KIF5C. Work from our laboratory demonstrated that KIF5C is essential for polarization of hippocampal neurons in culture, by linking the requirements of stable microtubules and IGF-1 receptor membrane insertion. Now, using “in utero” electroporation we have analyzed the consequences of KIF5C lack of function on cortex formation. Neurons electroporated with a shRNA targeting KIF5C at E14.5 failed to migrate to the upper cortical layers and accumulated at the ventricular/subventricular zones at E18.5. In control brains at P2, all neurons migrated to III/IV cortex layers. In contrast in neurons electroporated with a shRNA targeting KIF5C at E14.5 there is a significant number of cells restrained at the intermediate zone. We study the morphology of neurons migrating through the intermediate zone at E18.5 showed, in controls, bipolar cells migrating radially to the cortical plate. In brains suppressed for KIF5C cells at this region we found either multipolar or amorphous neurons forming a

highly disorganized tissue. These results indicate that KIF5C is important for neuronal migration and differentiation, including the “polarity switch”, essential for normal cortex formation.

Cellular and Molecular Neurobiology

P79.-Brain changes of serotonergic 5HT2C receptor and oxytocin expression after an acute body sodium depletion

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A temporal dissociation exists between sodium depletion (SD) and the appearance of sodium appetite (SA); and an inhibitory modulation of oxytocinergic and serotonergic (5HT) systems has been postulated. Our recent results also demonstrated a specific temporal pattern of serotonergic and oxytocin receptor mRNA expression (5HT2C and OTR, respectively), along different brain areas after SD. Our aim was to evaluate 5HT2C and OT proteins expression, during the delay of SA appearance after SD. Wistar rats were SD using furosemide combined with a low sodium diet, and 2h or 24h later were decapitated.Protein samples were extracted of dorsal raphe nucleus (DRN), subfornical organ (SFO), lateral parabrachial (LPBN), paraventricular nucleus (PVN) and supraoptic nucleus (SON), and then were analyzed by western blot. The OT+NP expression increased (p=0.001) after SD in the PVN in Comparison to control groups (CD). The 5HT2C expression significantly increased (p=0.0088) and decreased (p=0.0018) after SD along DRN and LPBN respectively, in comparison to CD. The 5HT2C expression in the SFO and the OT+NP expression in the SON did not change. However, none of these proteins within the different nuclei showed a temporal effect. Our results indicate that SD differentially change the expression of 5HT2C and OT-NP along PVN, DRN and LPBN suggesting that they are modulated by sodium status, allowing excitatory and inhibitory CNS signals integration in order to reach the water and sodium balance.

Cellular and Molecular Neurobiology

P80.-Role of the Piriform Cortex in the development of social behavior in mice

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The autism spectrum disorder is a group of pathologies characterized by social impairment and restricted and repetitive behaviors. Currently, the etiology of this disorder is not well understood. In autistic children, early social stimulation is one of the most effective treatments. In previous studies in our laboratory, the reduced sociability observed in a pharmacologically induced model of autism was reverted by early social stimulation. Positron emission tomography of the brain followed by immunohistochemistry and HPLC studies revealed that the piriform cortex (PC) has an altered glucose metabolism, increased neuronal activity and increased dopamine metabolism in autistic-like mice. Interestingly, as in social behaviors, early social enrichment reverted those parameters to levels similar to those observed in control groups. In this project we aim to further understand, first, the cellular and molecular alterations in the PC of animals with different sociability levels, and second, the

role of this structure on the development of social behaviors in mice. For the first goal, we will characterize the expression levels of dopamine Receptors D1 and D2 and oxytocin receptor (by qPCR), the levels of dopaminergic innervation and the identity of the c-Fos positive neurons of the PC (by immunofluorescence). For the second goal, we will evaluate the effects on sociability of mimicking or blocking the observed changes in dopaminergic function and/or neuronal activity in the PC.

Cellular and Molecular Neurobiology

P81.-Arylalkylamine N-acetyltransferase: "Nuclear translocation and potential role in response to blue light in retinal neuron cells"

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Aryalkylamine N-acetyltransferase (AANAT) is the key regulatory enzyme in melatonin synthesis. AANAT is present in the pineal gland, retina and other regions where is controlled by the molecular clock and light. The AANAT stability is regulated by cAMP increase promoting important changes in its activity. Vertebrate retina is a photosensitive tissue and is known that prolonged exposition to blue light (BL) causes to retinal damage and circadian clock disruption. In addition AANAT belong to GNAT-5 family together with histones acetyl transferases. Here we investigated the regulation of AANAT and histone 3 acetylation at lysine 27 (H3k27) in primary cultures of chicken embryonic retinal cells exposed to different L conditions. Cultures exhibited BL induction of AANAT as compared with dark controls (D). Interestingly AANAT showed a localization change, from the cytoplasm to nucleus, increasing in BL, and remain elevated in darkness 1 h after BL exposure. Furthermore, high levels of the phosphorylated enzyme were detected after the BL treatment comparated with the D control, in nuclear fractions obtained from primary cultures together with a significant increase in H3k27 levels after BL treatment. Results suggest that AANAT is a BL-induced enzyme in retinal neuron cells, promoting its phosphorylation and nuclear importation, likely playing important roles in nuclear function in response to BL exposure.

Cellular and Molecular Neurobiology

P82.-Effects of nuclear receptors PPARγ and RXR activation in NPC and OPC primary cultures

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CNS demyelination is a pathological process stemming from direct oligodendrocyte (OL) damage, while remyelination is the repair process by which oligodendroglial precursor cells (OPC) proliferate, migrate and mature into OL to restore myelin. RXRs are nuclear receptors forming homodimers, or else heterodimers with peroxisome proliferator-activated receptors (PPARs), which regulate OL differentiation and maturation. The aim of the present work is to study the single or joint activation of RXRγ and PPARγ by specific agonists 9 cis retinoic acid (RA) and pioglitazone (PIO), respectively, in neural progenitor cell (NPC) and OPC primary cultures. NPCs obtained from the SVZ of young adult rats and OPCs obtained from the cerebral cortex of newborn rats were treated with RA, PIO, PIO+RA or their vehicle for 4 days. In NPC cultures, results show that 5 µM PIO promoted an increase in the proportion of Nestin+/GFAP+ cells and the proliferation of NPC-derived PDGFRα+ cells. In

contrast, 10 µM RA inhibited PDGFRα+ cell proliferation. However, combined treatment of 5 µM PIO + 10 µM RA exerted effects comparable to those of single PIO treatment. In turn, in OPC cultures, 10 µM RA treatment revealed a differentiating effect on PDGFRα+ cells and an increase in their morphological complexity. These results suggest the participation of RXRγ and PPARγ in OPC proliferation and differentiation and may be thus considered possible therapeutic targets in the treatment of demyelinating diseases.

Cellular and Molecular Neurobiology

P83.-Intracellular trafficking of Diacylglicerol Lipase in Kinesin Light Chain knock-out neurons

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Endocannabinoid (eCB) signaling modulates axonal growth, guidance and synaptogenesis. Diacylglycerol lipase-α (DAGL-α) and -beta (DAGL-β) synthesize 2-arachidonoyl-glycerol (2-AG). 2-AG regulates the axonal growth cone-turning decision through the activation of the cannabinoid type 1 receptor (CB1R). Acquisition of precise neuronal connectivity requires a proper targeting and accurate spatiotemporal localization of both, CB1R and DAGL, in the surface of navigating axons.Although cargo delivery mediated by molecular motors is essential in developing neurons, the transport mechanism of the eCB system in developing axons is not fully understood. Our previous results showed significant impairment in CB1R axonal transport properties in neurons lacking the kinesin light chain 1 (KLC1) subunit of the anterograde motor kinesin-1. Defects in CB1R axonal transport triggers dysfunctions in eCB-dependent axonal growth. Here, we tested whether KLC1 deletion also affects the intracellular trafficking of DAGL-β. By live-cell imaging of fluorescent DAGL-β tagged vesicles we characterized the axonal transport properties of DAGL in transfected primary hippocampal neurons. Our preliminary data reveals that DAGL-β vesicles moves at slower speeds than CB1R vesicles and that KLC1 deletion impairs anterograde DAGL-β average velocity without affecting retrograde velocity. These results suggest that kinesin-1 could play a key role in both, DALG and CB1R intracellular trafficking.

Cellular and Molecular Neurobiology

P84.-Neuroprotective effect of FK506 against oxidative stress

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Immunophilins FKBP51 and FKBP52 bind the macrolide FK506. Previously, we reported that FK506 favours neurodifferentiation and the neuroregeneration. Here, we analyzed whether FK506 also shows neuroprotective action to oxidative stress. A rapid neuritogenesis was observed in undifferentiated N2a cells treated with 1 µM FK506 in the absence of trophic factors, including serum. Then, 250 µm slices from prefrontal cortexes from Balb-C mice (60 d) were prestabilized for 72 h and incubated for 4 h with 200 µM H_2O_2. Western blots revealed the induction of Hsp90, Hsp70, FKBP52 and p23, which was prevent by 1 h pretreatment with 1 µM FK506. While controls showed three phosphorylated isoforms of FKBP51, treatment with H_2O_2 only exhibited the least phosphorylated band. In turn, pretreatment with FK506 protected the phosphorylated isoforms, and treatments

with FK506 alone showed the intermediate phosphorylated band (reactive to anti-P-Tyr IgG), suggesting that this isoform may be responsible for the mechanism of action of the drug. Hypoxia was generated by stereotactic injection of 2 µl 50 mM CoCl2 in the prefrontal cortex of the right hemisphere, and the contralateral was used as control. The overexpression of chaperones was partially impaired by pretreatment with FK506. Rotarod and open field (AnyMaze) studies evidenced better and faster recovery of FK506-treated mice. This study shows for the first time the neuroprotective effect of FK506 against oxidative stress in nervous tissue.

Cellular and Molecular Neurobiology

P85.-SARA involvement in modulating TGFβ signaling during neural development

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Several events are necessary for proper neuronal development, such as cytoskeleton dynamics and endosome trafficking. SARA is a protein that binds to early endosomes; performing both traffic and signaling functions, as in the transforming growth factor β (TGFβ) pathway. In this sense, it has been described that SARA recruits Smad2/3, favoring the activation of this pathway; but it can also modulate the inactivation of TβRI by PP1c in both epithelial cells and cell lines. In addition, TGFβ signaling has been shown to specify the axon during neuronal development; however, the participation of SARA in this signaling pathway during development remains unknown. For this reason, we proposed to analyze the role of SARA in TGFβ signaling during neuronal development. Results obtained in cultures of hippocampal neurons, by FRET showed physical interaction between SARA and TβRI. In addition, performing experiments of loss and gain of function, we found that dominant-negative form of SARA (SARA-F728A) generates greater axonal growth and loss of axonal specification compared to control condition. Interestingly, this mutant alters its binding to the PP1c protein, keeping the TGFβ pathway over-activated. Also by FRET, we find that SARA-F728A has more interaction with PP1c and GADD34 than control, suggesting that SARA prevents TβRI dephosphorylation. These results suggest that SARA negatively modulates the TGFβ pathway, which seems to be a necessary requirement for proper axon specification.

Cellular and Molecular Neurobiology

P86.-Spontaneous electrical activity regulates axonal arbor growth in developing Zebrafish lateral line afferent neurons

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Neuronal circuits responsible for processing sensory information are established early in development through a combination of genetic programs and activity-dependent processes. A remarkable feature of this process is that it relies on stimulus-independent or “spontaneous” electrical activity (SEA) generated within sensory organs. In order to decipher the mechanisms by which SEA affects the assembly of developing sensory circuits, we used the Zebrafish (Danio rerio) lateral line system (LL). The LL allows fishes and amphibians to detect water motion

and pressure changes and consists of clusters of mechanosensory hair cells and non-sensory supporting cells. LL hair cells are innervated by afferent and efferent neurons, and share structural, functional and molecular similarities with hair cells in the vertebrate inner ear. Zebrafish LL afferent neurons exhibit SEA between 5 and 7 days post-fertilization (dpf), however its role in the assembly of LL circuit is still unknown. To answer this question, we silenced SEA in single LL afferent neurons by stochastic over-expression of inward rectifier K+ channels. At 5 dpf, suppression of SEA in single LL afferent neurons led to a decrease in both axonal arbor length and innervation area in the hindbrain. Our results provide an in vivo demonstration that SEA regulates axonal arbor growth and territory in the hindbrain, in developing LL afferent neurons.

Cellular and Molecular Neurobiology

P87.-ASIC1a channel and activation of ERK pathway

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ASIC channels are sodium channels activated by tissue acidosis and thus become active in many pathological conditions. ASIC1 is the most abundant ASIC subunit in the mammalian central nervous system. Physiologically, its activation is related to synaptic plasticity, learning and memory.ASIC1 channels in particular permeate not only sodium but slightly calcium ions, and so can contribute to intracellular calcium levels and neuronal injury in pathological conditions. Changes in regional pH levels in the brain have been observed in a number of neurological and neurodegenerative disorders and this event could lead to channel activation. In fact, ASIC1 channels have been lately implicated in several neurological diseases, as blocking this channel improves models of cerebral ischemia, Parkinson's disease, Huntington´s disease and ALS. Recently, amiloride was able to reduce huntingtin aggregates in cell lines and alleviate the pathology in HD mice models, reported to occur via an ubiquitin-proteasome mechanism. We decided to analyse the pathways activated by the channel. We used HEK cell lines and mouse primary neurons and analysed the ERK pathway. We showed, by using an ASIC agonist, and inhibitors that ASIC activation leads to the activation of the ERK pathway, via phosphorylation of ERK1 and ERK2 isoforms and translocation of the phosphorylated isoforms to the nucleus. Establishing the exact role of ASIC pathology could lead the way to therapies with specific channel blockers.

Cellular and Molecular Neurobiology

P88.-Effects of postnatal overfeeding and enriched environment over the brain reward system evaluated by feeding behavior test

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Consumption based on the rewarding properties of foods is a central contributor to the current obesity epidemic. Postnatal overfeeding (POF) is a well-known model of early-life induced obesity, and enriched environment (EE) has been shown to reduce the risk of obesity. Our aim was to analyze the positive influence of EE on the behavior towards sucrose in a model of POF rats raised in small litters (SL, 4 pups/dam) and control rats raised in normal litters (NL, 10 pups/dam) exposed from weaning to EE or standard environment. In PND85, a sensory-specific satiety (SSS) test was carried out using 10% (w/v) sucrose and maltodextrin solutions. SSS represent the decrease in hedonic pleasantness of a food (sucrose) after it is eaten. During the familiarization session of the test, EE increased sucrose and maltodextrin intake in SL rats ($p=0.001$). This was also observed in the pre-exposure to these solutions prior to the test ($p=0.002$). In the SSS test session no differences were observed in the intake of the maltodextrin solution whether the animals were pre-exposed to it or not. However, SL-SE rats ingested more sucrose only when they were pre-exposed to it ($p=0.007$), and EE prevented this effect in SL-EE rats. These results indicate that POF affects the hedonic value of sucrose in a repeated exposure, and EE may prevent this alteration. This study evidences that nutrition and environment during development may impact upon motivated behaviors toward food.

Cellular and Molecular Neurobiology

P89.-Abnormal neuron nuclear morphology after transgene suppression in a conditional TDP-43 mouse model of neurodegenerative disease

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Dysregulation of TDP-43 is a key feature of frontotemporal dementia (FTD) as well as amyotrophic lateral sclerosis (ALS). Previously, using a transgenic mice conditionally overexpressing human wild-type TDP-43 protein (hTDP-43-WT) we analyzed the region-specific neuronal loss. We found a decrease in CA1 and dentate gyrus (DG) NeuN+ cells width accompanied by decreased neuronal number, indicating mild neurodegeneration after 1 month transgene (TG) expression (1mo). In this study, we evaluated in this model the nuclear morphology of neurons from hippocampal regions (DG and CA1), and somatosensory cortex layers after a TG suppression protocol. We found an increased percentage of abnormal nuclei in the suppressed group compared to controls and 1mo mice in all analyzed regions. This suggests that the cellular mechanisms coping with hTDP-43 overexpression and recovery after suppression might differ. In this context, we are currently assessing how TG suppression modulates neurodegeneration by evaluation of neuronal survival. Additionally, we studied the impact of corticospinal tract degeneration (observed in hTDP-43-NLS mice expressing a cytoplasmically-localized form in the forebrain) on lower motor neuron (LMN) health in the spinal cord (SC). Using Nissl staining, we analyzed LMN area in the anterior horn from different SC segments and found no differences in TG TDP-43-NLS mice compared to controls. In summary, these results contribute to our understanding of FTD/ALS pathology.

Cellular and Molecular Neurobiology

P90.-Hippocampal glucocorticoids receptors mediate a sex-biased microRNAs profile expression in mice

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Glucocorticoid through the activation of Glucocorticoids receptor (GR) can produce changes in neuronal morphology in important brain regions implicated in cognitive performance such as the hippocampus. These morphological changes in neurons are final consequences of transcriptomic and proteomic reorganization in face of a new stressful environment; however, there is no much information about the influence of GR in these processes. In this study we evaluated the differential expression of microRNAs profile in mice hippocampus by using the Nano String platform by comparing two Knock out (KO) mouse models for the GR. One of these models (EKO) involved selective KO for hippocampus (n = 24) while the other is globally KO (NKO) in brain neurons (n = 25). Interestingly, by taking the ratio E-Wild type/EKO and using bioinformatic analyzes, it was identified that transcriptional processes modified by the presence of the GR in the hippocampus show sex-bias. It was shown that the levels of 54 microRNAs are significantly modulated by the presence of GR in female mice in contrast to only 8 microRNAs in male mice. In contrast, in NKO model just only 16 microRNAs differentially expressed were identified in females and only 8 microRNAs in males. Finally, by analysis of microRNA-mRNA interaction networks, the potentials mRNA target and the pathways regulated by these microRNAs were identified, highlighting transcripts involved with the cytoskeleton remodeling.
This work was supported by FONDECYT 119-0899 and ENL0118-01

Cellular and Molecular Neurobiology

P91.-Climbing fiber patterning is impaired by angiotensin II type 2 receptor blockage on postnatal cerebellum
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The Renin Angiotensin System (RAS) blockers are associated with fetopathy during the third trimester. Ang II AT2 Receptor has been related to a neuronal differentiation during fetal and postnatal development. In cerebellum, AT2R are located only in the Purkinje cells (PC). PCs guide afferent topography to establish the final neuronal circuit. Changes in PC morphology can result in climbing fiber (CF) multi-innervation or mispatterning. We aim to determine the effect of prenatal AT2R blockage on CF connections and PC topology during postnatal development. Wistar rats were implanted mini-osmotic pumps subcutaneously with AT2 antagonist (PD123319) and vehicle during pregnency. Morphological analysis by indirect immunofluorescence was performed on P5, P7 and P15. The results were at P5, PC number was significantly increased ($p<0.001$), non-significant decrease in the arborization length and VGLUT2+ puncta innervating the PC somata. At P7, a delay in PC morphology development, significant increased in VGLUT2+ ($p<0.01$) and decrease in the dendritic tree ($p<0.05$). At P15, VGLUT2+ and PC morphology were normalized. These changes do not compensate the PCL length ($p<0.05$) or the CF territory ($p<0.05$) both significantly increase on treated animals. The results demonstrate changes in PC topology and CF mis-patterning on treated pups. We observed that some parameters were still alter at P15. This study supports the participation of AT2R on cerebellar cortex organization.

Cellular and Molecular Neurobiology

P92.-Sex chromosome complement regulates Dnmt3a-gene expression in the anterior amygdala of developing mouse brain

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Both hormonal and genetic factors interact to induce long lasting effects on sexually dimorphic gene expression in the mouse brain. Epigenetic mechanisms, such as DNA methylation, have recently been proposed as mediators of hormonal-dependent sexual differentiation of the brain. DNA methylation involves the addition of methyl groups by DNA methyltransferase enzymes (Dnmts) as well as the recruitment of methyl-binding proteins (such as MeCP2) and usually leads to gene repression. In order to study whether DNA methylation also mediates sex chromosome-dependent factors involved in sexual differentiation of the brain we used the "four core genotypes" mouse model which allows the evaluation of gonadal sex, sex chromosome complement, and their interaction. We analyzed the mRNA expression of Dnmt3a, Dnmt1 and Mecp2 in vivo (anterior amygdala) and the interaction of hormonal and sex chromosome complement in vitro (primary neuronal cultures). Dnmt3a expression levels were higher in the anterior amygdala derived from XX embryos compared to XY, irrespectively of gonadal sex. No differences were observed in the expression of Dnmt1 and Mecp2. No significant effect of E2 or DHT on Mecp2 was seen in vitro. These results suggest that sex chromosome complement might determine a higher "de novo DNA methylation" in specific areas of the XX brain. More experiments are required to understand the role of X/Y chromosomes in the epigenetic changes involved in the sexual differentiation of brain.

Cellular and Molecular Neurobiology

P93.-Adipose-derived mesenchymal stem cells and magnetic nanoparticles: different tools combined to promote sciatic nerve regeneration after injury

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Neuropathies constitute a major issue in public health with high prevalence worldwide. Patients' poor clinical evolution turns these affections into a crippling disease, which is why the development of new regenerative therapies is of great importance. Wallerian degeneration is an efficient animal experimental model in mimicking the impact of peripheral nerve lesion to shed light on possible regeneration strategies. In this context, the aim of the present work was to test whether magneto targeting, a nanotechnological strategy to mobilize magnetic nanoparticles (MNP), can help adipose-derived mesenchymal stem cell-loaded MNP (AdMSC-MNP) reach specific tissue guided by an external magnetic field and thus improve the regenerative ability of AdMSC upon sciatic nerve lesion. To test our hypothesis, AdMSC were extensively characterized, and MNP internalization by AdMSC as well as AdMSC-MNP arrival at the injured nerve were evaluated through microscopy and magnetometry. Finally, cell transplantation effects on regeneration were evaluated both in terms of nerve morphology and conduction. Our results show that AdMSC can internalize 2 to 4 pg MNP/cell and that AdMSC-MNP magneto targeting enhances cell arrival exclusively at the lesion site and their beneficial effects on sciatic

nerve regeneration. In short, our results prove that magneto targeting of AdMSC-MNP constitutes a novel and valuable tool to promote nerve regeneration by enhancing AdMSC arrival at the lesion site.

Cellular and Molecular Neurobiology

P94.-Participation of p75NTR in a mouse model of Choroidal Neovascularization

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In industrialized countries, the most frequent cause of blindness in the elder population is age related macular degeneration (AMD). In the wet form of AMD, neuronal demise is thought to be a consequence of the inflammatory response and the disruption of retinal architecture by proliferating vessels. However, the cells involved and the mechanisms underlying these processes still remain cryptic. It is known that the p75 neurotrophin receptor (p75NTR) participates in multiple vascular disorders, inflammation and neurodegeneration. This study aims to investigate the role of p75NTR in vascular and neuronal alterations in a mouse model of laser-induced choroidal neovascularization (CNV). Our results show a significant increase in p75NTR protein expression in retinal extracts of CNV mice by Western blot assay 7 days after the insult. Immunofluorescence staining on choroidal whole mounts evidenced p75NTR labeling in macrophages (F4/80 positive cells), but not in pericytes (NG2 positive cells), nor in endothelial cells (isolectin IB4 positive). Unlike neurons, Müller glial cells showed a significant p75NTR expression increase in the injured area on retinal section of CNV mice. Notably, the CNV protocol in p75NTRKO mice exhibited reduced visual impairment compared to wild type mice, evaluated by electroretinography. These results suggest a possible involvement of p75NTR in neuro-vascular alterations. Undergoing experiments will determine if p75NTR is a relevant target for AMD.

Cellular and Molecular Neurobiology

P95.-Dopaminergic neuroprotection induced by yerba mate: experimental evidence in hemiparkinsonian animals

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Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects the dopaminergic neurons of the substantia nigra, producing a decrease of dopamine in the striatum. Currently, although there are no

preventive therapies for PD, a case-control study revealed that the consumption of yerba mate (YM) has an inverse association with the risk of developing PD. The consumption of YM is widely popular in our region and it was shown to provide numerous health benefits. We propose to characterize the YM extract and evaluate if the consumption of YM provides a benefit on the survival of dopaminergic neurons. The YM extract was obtained by "cebada simulada" and its stability was determined by HPLC. One group of mice received water or YM (MATE) for 2 months before being lesioned with 6-OHDA in the striatum. Another group received water or YM infusion diluted ½ in water (dilMATE) for 4 months before the injury. After lesion, mice continued 1 more month with each treatment. Immunohistochemical evaluation of tyrosine hydroxylase (TH) indicated that treatment with MATE did not have any effect on the survival of dopaminergic neurons. On the other hand, the area of remaining TH+ terminals was 12.75 % higher in the MATEdil group compared to the animals treated with water. Our results suggest that this neuroprotective effect could be beneficial to retard the evolution of the neurodegenerative process of dopaminergic neurons in PD patients.

Cellular and Molecular Neurobiology

P96.-A critical period for experience-dependent plasticity in neurons born in the aged hippocampus

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The aging brain displays a generalized decline in cognitive capacity and circuit plasticity, including a decline in the production of adult-born hippocampal neurons. Morphological development of new dentate granule cells (GCs) is also affected by age. However, their functional properties and integration to the circuit along maturation remains unclear. We performed whole-cell recordings in 8-month old (8M) Ascl1(CreERT2);CAG(floxStopTom) mice to assess intrinsic properties, firing behavior and afferent excitatory connectivity in adult-born GCs labeled with Tomato. We found that the functional properties and connectivity of these neurons also develop in a slow manner. Despite the delayed maturation, new GCs in aging mice display a remarkable potential for structural plasticity. Retrovirally labeled 3-week-old GCs in middle-aged mice are small, underdeveloped and disconnected. Notably, we found a critical period during the second week of new GCs development in which they display a higher sensitivity to experience. A 7-day exposure to an enriched environment (EE) induced substantial dendritic growth, spine formation and a significative increase in the number of filopodia of CA3 boutons indicating that experience boosts both input and output connectivity. Moreover, electrophysiological recordings showed that a brief exposure to EE accelerates intrinsic electric properties and integration of new GCs.

Cellular and Molecular Neurobiology

P97.-Activation of D1R reduces the Kv1.3 current and contributes to the hypercholinergic state of parkinsonism

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Balanced actions of dopamine (DA) and acetylcholine (ACh) shape striatal function. In Parkinson's disease (PD) this balance is lost, leading to a hypercholinergic state. Striatal cholinergic interneurons (ChIs) are the main source of striatal ACh. Previously we found that ChIs are hyperexcitable in a mouse model of PD as a result of a

reduction in a current mediated by Kv1.3 channels, which is not explained by reduced channel expression. Our aim is to identify the mechanisms that underlie this hyperexcitability. With ex-vivo electrophysiological recordings, we found that SKF81297 (SKF), a DA D1-type receptor (D1R) agonist, increases the excitability of ChIs, and this effect is occluded by Margatoxin (MgTx), a blocker of Kv1.3 channels. The reduction in the current after application of SKF is also occluded by MgTx, suggesting a shared signaling pathway. Preliminary results suggest that this common pathway is adenylatecyclase (AC) dependent, since activating it with Fosrkolin increases the excitability and reduces the current in ChIs in the same way as SKF and MgTx do, and either of the effects are occluded by them. Our results suggest that the activation of D1R promotes the activation of the AC and, probably through PKA, induces the reduction of the Kv1.3 current and the subsequent hyperexcitability of ChIs. Further experiments in a mouse model of PD will be necessary to evaluate if an alteration of this pathway produces the ChIs hyperexcitability observed in this condition.

Cellular and Molecular Neurobiology

P98.-Effect of Nitro-Oleic Acids in a mouse model of Oxygen-Induced Retinopathy

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Inflammation, oxidative and nitrosative stress are involved in Neovascular retinopathies (NR). Although, VEGF inhibitors have been established as the mainstay of current treatment, the clinical benefits have not always been successful. Moreover, Nitro-fatty acids are important electrophilic signaling mediators with anti-inflammatory and cytoprotective properties (Keap1/Nrf2 pathway). Here, we hypothesized that Nitro-oleic acid (NO2-OA) can modulate the antioxidant response in NR. Initially, intraocular (i.o.) and intraperitoneal (i.p.) injection of NO2-OA toxicity was assessed by scotopic electroretinography (ERG) and H&Eo staining. C57BL/6 adult mice were i.o. injected at P0 with PBS, vehicle and 5µM of NO2-OA, and i.p. at P2, P5, P8, P11 and P14 with PBS, vehicle and 15 mg/Kg of NO2-OA. The a- and b-waves from ERG were recorded at P3, P7 and P15. No differences in ERG signals were observed. Thus, the Oxygen-Induced Retinopathy (OIR) model was carried out. Briefly, C57BL/6 mice were exposed to 75% O2 from P7 to P12, and then brought to room air for additional five (P17) or nine days (P26). Some OIR mice were i.o. injected at P12 with 5 µM of NO2-OA or vehicle and i.p. at P14, P17, P20 and P23 with 15 mg/Kg or vehicle. Western blot of neural retinas showed significant changes in glutamine synthetase, VEGF-A and GFAP levels at P17 and P26 in OIR mice treated with NO2-OA respect to vehicle. These findings indicate that NO2-OA could be beneficial for retinal cells in the NR.

Cellular and Molecular Neurobiology

P99.-Identifying molecular mediators of the effects of cerebellar neuroinflammation on sociability: relevance for autism

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One of the main symptoms of autism spectrum disorder (ASD) is the difficulty to engage socially. Although the pathophysiological bases of ASD are unknown, there is vast evidence on the role of the cerebellum in the development and expression of the disorder. We have reported that inflammation in the lobule 7 of the mouse

cerebellum, induced by the stereotaxic injection of lipopolysaccharides (LPS), results in a decrease in sociability 24 hours after. This effect is prevented completely by dexametasone and partially by ibuprofen. The aim of this project is to identify mediators of these effects by detecting inflammatory molecules that can alter sociability in ASD. To perform this, groups of adult male CF1 mice were injected with either 10ng LPS (LPS group) or saline (SAL group) in cerebellum lobule 7. 30 minutes before, both groups will receive dexamethasone, ibuprofen, or saline. Thus, the experimental design evaluates the effects of drugs (DEXA; IBU; SAL) on the treatment (LPS; SAL). In these animals, we observed that DEXA has a more pronounced effect than IBU in blocking microglia activation. We will further characterize the response, by identifying the expression of pro and anti-inflammatory cytokines in the cerebellum of LPS injected and anti-inflammatory treated mice. To this aim, we will quantify the expression of pro and anti-inflammatory cytokines by RT-PCR. The goal of this work is the identification of possible therapeutic targets for individuals with ASD.

Cellular and Molecular Neurobiology

P100.-Shiga toxin 2 (Stx2) from enterohemorrhagic Escherichia coli (EHEC) produces cerebellar impairment of the vascular unit with inflammatory involvement

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Stx2 from EHEC produces Hemolytic Uremic Syndrome and neurologic alterations including cerebellar involvement in patients. The aim of this study was to determine the mechanisms by which Stx2 causes cell damage in the cerebellum. Mice were injected intravenously with 1ng of Stx2 or 100 µl of saline. Fixed cerebellums were subjected to staining with lectins (microvasculature profile) and immunofluorescence with anti-GFAP (astrocytosis marker) and anti-MBP (myelin protein marker). ELISA kits measured TNFα and IL-10. Stx2 reached the Purkinje and granular layers. Stx2 significantly: decreased the area occupied by the microvasculature (12.58 ± 0.73 Control vs 7.71 ± 0.72 Stx2, day 2, in µm2); increased the expression of GFAP (11.3 ± 0.3 Control vs 17.97 ± 0.87 Stx2, day 2, and 12.11 ± 0.67 Control vs 14.8 ± 0.6 Stx2 day 4, in IOD),and decreased the expression of MBP (67.6 ± 2.4 Control vs 35.4 ± 0.9 Stx2, day 2, and 62.6 ± 2.5 Control vs 46.2 ± 1.4 Stx2 day 4, in IOD); $p<0.001$. Stx2 increased the expression of TNFα at day 2 (4.8 ± 1.7 Control vs 12.4 ± 2.1 Stx2, in pg/mg protein), while IL-10 expression was increased at day 4 (25.05 ± 3.9 Control vs 67.2 ± 10.8 Stx2, in pg/mg protein); $p<0.001$. Finally, Stx2 damaged the cells that integrate the vascular unit, with inflammatory involvement. Further studies are being conducted to elucidate the observed cell events.

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Cellular and Molecular Neurobiology

P101.-Expression and cellular function of KCNQ channels in the eye

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KCNQ subunits (1 to 5) form voltage-gated potassium channels. They are responsible of the M-current that regulates neuronal excitability in the CNS. KCNQ4 and -5 expression has been reported in the retina where could participate in the visual processing. Our aim was to investigate the expression and function of KCNQ channels in different tissues of the eye, employing KO mice for subunits 3 to 5. By KO-controlled immunofluorescence, we found a weak labeling of KCNQ4 in retinal pigmented epithelium (RPE) cells and the ciliary body (CB). KCNQ4 signal in RPE was stronger in the area adjacent to the CB and located in the apical membrane of the cells. In the CB the signal was placed in the basal membrane of the pigmented epithelium (PE) cells. KCNQ5 was found neither in the retina nor RPE or CB. Finally, KCNQ3 was observed in non-pigmented epithelium (NPE) cells of the CB. Gene expression analysis by RT-PCR showed that all KCNQ subunits were present in RPE/retinal tissue while in CB were only KCNQ1, -4 and -5. This profile was altered in KCNQ4 KO mouse with the appearance of KCNQ2. By patch-clamp, we observed the M-current in 40% of the RPE cells while it was absent in the KCNQ4 KO mouse. In CB, the M-current was present in NPE cells, however it could not be analyzed in PE cells. NPE cell-currents were preserved in KCNQ4 KO mouse. In conclusion, KCNQ4 may participate in the homeostasis of K+ in the subretinal space and the ciliary body, contributing to transepithelial transport.

Cellular and Molecular Neurobiology

P102.-Histone acetylation in reactive astrocytes: Is microglia the triggering "sparkle"?

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Astrocytes are essential in keeping CNS homeostasis and bringing metabolic support to neurons. It was shown that microglia activated by Lipopolysaccharide (LPS) promotes astroglial polarization to the pro-inflammatory and neurotoxic phenotype A1. We showed that this polarization is TLR4/NFκB dependent (Rosciszewski et al., 2018).In different peripheral cell types, NFκB can recruit enzymes with chromatin remodelling functions (e.g. histone acetyltransferase p300). We here aimed to understand if NFκB activation primes chromatin in A1 astrocytes through histone acetylations. We used primary cultures of glial cells obtained from C57BL/6 mice. After microglia depletion, cultures were exposed to LPS 25ng/ml for different times. NFκB activation and histone 3 acetylation (H3ac) was evaluated by immunofluorescence and immunoblotting. Astrocyte or microglia were identified as GFAP+ or IBA1+ cells respectively. Nuclear localization of NFκB subunit p65 was used as parameter of activation. Our results show that NFκB is activated in astrocytes at 1 h LPS (not before) remaining active for at least 6 h. Activation at 1 h significantly increased when microglia was added to cultures. However, we were not able to detect global changes in H3ac after LPS exposure in microglia-depleted primary cultures of astrocytes. We conclude that microglial cells may be the key to induce chromatin remodelling by facilitating NFκB activation.

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Cellular and Molecular Neurobiology

P103.-Posttraslational modification of tubulin by tyrosine analogues alters mitochondrial transport mediated by molecular motors

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The C-terminal tyrosine (Tyr) of the α-tubulin chain is subjected to post-translational removal and re-addition in a process termed the "detyrosination/tyrosination cycle". We showed in previous studies, using soluble rat brain extracts, that L-3,4- dihydroxyphenylalanine (L-Dopa) and L-phenylalanine (Phe) are incorporated into the same site as Tyr and that such incorporation also occurs in living cells. To study the functional effects of the incoprporation of Tyr analogues into α-tubulin, we treated primary rat hippocampal neurons with L-Dopa or Phe. We observed a reduction in the number of mitochondria in distal segments of the axon and alterations in the mitochondrial traffic along axonal microtubules. We also observed an abnormal interaction between L-Dopa enriched microtubules and molecular motors that participate in organelles transport. We hypothesized that these alterations could be associated with neuronal disorders observed in Phenylketonuria patients and Parkinson's disease patients treated with L- Dopa for prolonged periods.

Cellular and Molecular Neurobiology

P104.-Effects of copper overload on cholesterol synthesis and APP cleavage

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Copper (Cu) is involved in the development of many neurodegenerative disorders. Brain cells depend entirely on cholesterol(Cho) in situ synthesis. It was demonstrated that high plasma Cu concentration is in line with rises in Cho levels(Armstrong, 2001; Arnal, 2013). Many works showincreases in the transcription of genes related to Cho synthesis in human macrophages and in Jurkatcultured cells exposed to Cu (Svensson, 2003; Gutiérrez, 2013).The amyloid precursor protein (APP) is housed in Cho rafts. It has been proven that increases in Cho levels would favor the processing of APP towards the formation of Aβ peptides (Liu, 2009). The objective was to evaluate if Cu overload could favour Cho synthesis in cultured neurons (SHSY5Y), inducing the processing of APP to the amyloidogenic pathway. Cu levels were evaluated by atomic absorption spectrophotometry. The synthesis of Cho was analyzed using radioactively labeled acetate by thin layer chromatography (TLC) and Cho in plasma membrane by gradient de Ficoll. The protein levels of 3-hydroxy-3-methyl-glutaryl-CoA reductase and APP was evaluated in cellular homogenates and levels of Aβ peptides in culture medium by western blot. HMGCR expression was assessed by qPCR. Neuron cells exposed to Cu overload showincreased levels of HMGCR.Higher levels ofthe novo synthesized and membrane Cho were observed in Cu treated cells than in control ones. Finally, there were no changes in APP levels. Currently, we are analyzing the levels of Aβ.

Chronobiology

P105.-As the Brain's Soldiers Grow Older: Aging Microglia within the Pineal Gland

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Microglia are resident immune cells of the central nervous system (CNS). They not only defend the CNS from insults, but they also contribute to the brain ontogeny and homeostasis. In the developing pineal gland (PG), microglia are a dynamic population that make active contact with pineal precursor cells and other constituent elements. These interactions modulate the fate, density and activity of pineal elements as they develop. For the aging CNS, microglia shift into an altered phenotype. In this study, we tried to characterize the aging microglia in PG from 18-month-old rats. Our analysis against 3-month-old rats showed a slight but significant decrease in the density of microglia-like Iba1+ cells in the old PG. Their proliferative capacity was also significantly reduced based on the levels of the nuclear marker PCNA. However, heterogeneity in PCNA expression among Iba1+ cells was observed at both ages. In the aged Iba1+ cells, we noted a spectrum in the expression pattern of the lysosomal marker ED1 from discreet cytoplasmic ED1+ bodies to enormous and deforming ED1+ structures. Also, we found that the density of the precursor-like Pax6+ cells decreased during aging, but the percentage of contacts between Iba1+ and Pax6+ cells remained stable from adulthood to old age. Our results illustrate some of the changes experienced by the pineal microglia during aging. These impacts within the pineal microenvironment could affect the overall physiology of the gland as it ages.

Chronobiology

P106.-Glial contribution to circadian structural plasticity in pacemaker neurons of Drosophila melanogaster

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Circadian clocks are present in almost all organisms, as they provide a way to adjust their physiology to the daily environmental changes triggered by the rotation of the planet. In the brain of D. melanogaster, this clock comprises 150 neurons that are divided in several clusters according to their anatomical location. Among these groups, the small ventral lateral neurons (sLNvs) are considered the “main pacemaker”, as they govern circadian activity patterns in constant darkness. The sLNvs dorsal projections contact specific neuronal clusters differentially across the day. These terminals cyclically change their structure, displaying a highly arborized and desfasciculated architecture in the morning, to a less branched structure in the early night and to an even more retracted form before dawn. These changes modify the way the pacemaker circuitry is wired, but its effects on animal behavior and the molecular basis that control this process are only recently begun to be explored. A few years ago our laboratory described that a functional glial clock is necessary for the coordination of this phenomenon. In this work, we describe in depth this neuronal-glial interaction as a function of the time of day and found that these termini contact directly with two different glial subtypes (astrocyte like and ensheathing glia) and that the contacts with the ensheathing glia are time-of-the-day dependent, suggesting that this subtype actively contributes to the remodeling process.

Chronobiology

P107.-Processing bodies and Stress granules oscillate in Neuro-2a cells and mouse fibroblasts

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Processing bodies (PB) and Stress Granules (SG) are membraneless organelles involved in mRNA storage, processing and decay. Whereas PB are constitutive organelles, SG are assembled in response to stress. We have previously shown that SGs induced by oxidative stress and PBs display daily changes in their number and size in synchronized NIH3T3 cultures. Here, in order to determine whether these changes are controlled by a biological clock, we analyzed SG and PB between 8h and 68h postsynchronization with a higher sampling frequency. We induced SG formation by oxidative stress with sodium arsenite. We also studied the temporal expression profile of p-eIF2α and eIF3 (factors involved in SG aggregation) by Western blot. For this purpose N2a cells and fibroblasts were grown and then arrested to prevent cell cycle progression. They were then synchronized and harvested at different times. We confirmed that cells were in quiescent state by flow cytometry. We performed ICC with anti-eIF3 primary antibody, a known SG marker, in NIH3T3 fibroblast and we used two PB markers: anti-DDX6/P54/RCK and anti-GE-1/HEDLS in double immunolabelling experiments in N2a cells. Metacyle analysis revealed that both SG and PB were rhythmic for 2 cycles with periods of about 24h for all variables analyzed (Number per field, Area and Signal intensity). The p-eIF2α and eIF3 proteins presented slight changes over time and therefore would not be responsible for generating the changes observed in SGs.

Chronobiology

P108.-A metabolic oscillator controls temporal changes in lipid metabolism and redox status in tumor cells.
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Biological clocks even present in immortalized cell lines, regulate physiological processes in a time-dependent manner, driving transcriptional and metabolic rhythms. The molecular clock controls the expression of activators (BMAL1), repressors (PER1, 2, REV-ERB) and clock-controlled genes (Choline Kinase) along 24hs. REV-ERBs are involved in tumorigenesis and its synthetic agonist SR9009 affects the metabolism and cell viability in vivo. The disruption of circadian rhythmicity in modern life (ex. shiftwork, jetlag) may promote higher cancer risk and metabolic disorders, but little is known about the biological clock function in tumor cells. Here we studied metabolic rhythms and its link with the molecular clock in two models of human tumor cell lines: the glioblastoma T98G and hepatocarcinoma HepG2 cells. In T98G cells we observed rhythms on redox state and glycerophospholipids (GPLs) metabolisms. Also, the temporal changes in the redox cycles were altered after Bmal1 knock-down. SR9009 treated cells exhibited increased lipid droplets (LDs) levels and decreased ROS and proliferation. HepG2 cells displayed significant circadian rhythms in the content of clock genes and CHOK proteins, in the ratio of endogenous GPLs (PC and PE) and in LDs levels. When the circadian clock was damped LDs and CHOK protein rhythms were damped out. Our results suggest a significant cross-talk between the molecular and the metabolic clocks in proliferating tumor cells from either, brain and liver.

Chronobiology

P109.-Drosophila clock neurons as a model to explore the selective vulnerability to huntingtin polyQ elongation
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One of the hallmarks of polyglutamine (polyQ) diseases is the selective vulnerability of different neurons in spite of ubiquitous expression of the pathogenic protein. The reasons behind this specificity underlying neurodegeneration is still an unsolved mystery. It has been reported that the two circadian clusters of lateral ventral neurons (LNv) of Drosophila melanogaster respond differently to the elongation of the polyQ tract of huntingtin (Htt) protein. It has been shown that while HttpolyQ protein functionally ablates the small LNvs (sLNvs) subgroup, the large LNvs (lLNV) remain unaltered. Our goal is to explore this differential response of LNvs to the HttpolyQ. In order to do this, we are studying morphological phenotypes and the consequences over the behaviors these neurons command. Our preliminary results regarding the morphology of the LNvs under the expression of HttpolyQ in young flies fit well with the published literature: sLNvs present protein accumulations of HttpolyQ and lLNvs do not. However, in aged flies lLNvs also show HttpolyQ protein aggregation, both in the somas and on their projections. These results suggest that, although the reported differential sensibility between the two neuronal groups exists, lLNvs are not immune to HttpolyQ protein aggregation. We will also show preliminary data regarding the effect of downregulating the fly endogenous huntingtin in LNvs. dHttRNAi expression in LNvs impairs circadian rhythmicity and affects sleep behaviour.

Chronobiology

P110.-Circadian control of postmating behaviors in Drosophila females
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Rest-activity cycles are common to both males and females of Drosophila melanogaster. However, there are some important sex differences related to the timing of the resting period during daylight hours. Usually, circadian studies focus on males, and thus temporal organization of female locomotor activity has received much less attention. One of its interesting aspects is that it undergoes important changes after the female has mated. Furthermore, the traits that appear (such as egg-laying) also seem to be controlled by the clock. We are interested in studying how the circadian clock integrates information from both environmental cues and internal (mated) status in order to control post-mating behaviors such as the daytime sleep and oviposition. Recently, it was shown that the activity of a group of clock neurons called DN1s is sexually dimorphic and has a major effect on the sleep–wake profile in males and females. Given the implications for the circadian network of a functional DN1, we inquired whether affecting the molecular clock, particularly in these neurons, alters female post-mating behaviors. We downregulated clock genes exclusively in DN1p neurons. We tracked fly motor activity and studied oviposition at the level of single individuals, using devices built and vallidated in our lab. We have found that functional clock in DN1 is neccesary to control daytime sleep but not rhtymic oviposition.

Chronobiology

P111.-The role of orsai in circadian rhythms and aging
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All organisms have a circadian clock that regulates different physiological, metabolic and behavioral processes. Understanding how this clock is related to the cell basal metabolism, and how it is affected over time under normal conditions is important, since it can provide cues regarding how its homeostasis influences neuronal aging. Through a behavioral screen, a new gene called orsai (osi) was identified, whose partial dysfunction affects circadian pattern of locomotor activity in middle-aged adults. ORSAI belongs to the LYR I family, and yet it localizes primarily within the nucleus, it appears to play an important function in lipid catabolism. Further evidence suggests that it is the ortholog of the ETFRF1 gene in vertebrates. In the present work, osi´s relevance in circadian neurons was evaluated. Partial osi dysfunction in PDF neurons lengthens the period in young and middle-aged flies, but causes arrhythmicity in middle-aged flies. The expression of the human ortholog ETFF1 in PDF neurons leads to the partial rescue of the observed phenotype. Interestingly, OSI was only detectable in the cytosol of l-LNvs, allowing to link the effect of osi depletion to a function in those circadian neurons.

Chronobiology

P112.-Temporal control of tumor growth in nocturnal mammals: impact of the circadian system
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Perturbations of the circadian clock function have a profound impact on numerous cellular pathways and thereby likely to contribute to many of the hallmarks of cancer. This circadian disruption between the endogenous circadian clock and external time has been correlated with increased cancer risk. However, little is known about the circadian clock function on tumor growth regulation. Here we investigate the day/night differences in the growth rate of peripheral nervous system tumors after the injection of A530 cells isolated from NPcis (Trp53+/-; Nf1+/-) heterozygous mice. First, synchronized A530 cultures exhibited temporal fluctuations in levels of PER1 protein, levels of ROS and susceptibility to Bortezomib chemotherapy. Secondly, A530 or melanoma B16 cells injected on C57BL/6 mice at the beginning of the day or the night showed a higher tumor growth rate when mice were injected at night as compared with those injected at the beginning of the day in animals maintained in a 12:12 LD regular cycle as well as when they were released to constant dark after LD synchronization and injected at the beginning of subjective day or night. Lastly, when we examined the role of the molecular clock activator Bmal1, a higher tumor growth rate was observed when Bmal1 expression was diminished by CRISPR/Cas9 in A530 cells (A5) compared with controls. Our observations strongly suggest an important circadian regulation on tumor growth mainly dependent on the host state.

Cognition, Behavior, and Memory

P113.-Object recognition reconsolidation in mice: What's the hippocampus deal?
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Object recognition tasks require the animal to distinguish between a previously experienced object (ie. familiar) and a novel one. The hippocampus' specific role supporting this memory has been largely debated.

Here, we study hippocampal role in object memory reconsolidation, the process by which new information can be integrated into a previously consolidated memory. Several studies show that for this plasticity process to occur there must exist a mismatch between the animal's previous expectation and the current experience. We aimed to establish what constitutes a behaviorally relevant mismatch for hippocampus-dependent reconsolidation to take place. With this goal, male mice were trained in the Novel Object Recognition (NOR) task and subject to different reexposure protocols. Intra-hippocampal sulfasalazine, an inhibitor of the NF-kB pathway, or sodium butyrate, an inhibitor of histone deacetylases (HDACs), were administered to reveal the destabilization of the memory trace. Amongst the different protocols tested, we found that only those including the familiar object were effective in triggering destabilization, shedding light on which components of the memory are supported by the hippocampus.

Cognition, Behavior, and Memory

P114.-Immunomodulation approach aimed to control neuroinflammation, amylod-beta aggregation and cognitive deterioration in a rat model of AD-like pathology

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The preservation of cognitive function during ageing has emerged as one of the major medical challenges of the 21st century. A fundamental question is why some individuals' age with their cognitive function relatively intact whereas others decline and develop Alzheimer's disease (AD). Early studies suggested that neuronal loss is a feature of the ageing brain. However, with the advent of stereological neuronal quantification, it became clear that neuronal cell number is preserved in ageing human brain, declining only in the setting of neurodegenerative disease. Substantive evidence indicate that CNS pro-inflammatory mechanisms has been implicated in the aging process and in the pathological changes associated with AD. The main goal of the present study is to investigate the immunomodulatory properties of a pregnancy derived peptide (preimplantation factor, PIF) to successfully alleviate AD pathology and cognitive impairment in a rat model of AD. Previous studies reported that PIF effectively regulates systemic immunity leading to neuroprotective protection, reversing neuroinflammation and promoting neuronal repair. However, PIF has never been tested in AD. We demonstrated that chronic treatment with PIF decrease Aβ hippocampal accumulation in our 18-months old Tg rats, reducing pro-inflammatory cytokines levels (IL-6, Il-1β, COX-2) and preserving cognitive functions. Our results suggest that PIF may represent a potential agent for therapeutic treatment of AD-like pathologies.

Cognition, Behavior, and Memory

P115.-Repeated cold exposures controls hippocampal inflammation and prevent cognitive impairment in AD-like rat model

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While research into cold-induced neuroprotection is enjoying newfound interest in chronic neurodegenerative disease, the scope of the potential utility of therapeutic hypothermia (TH) across the field, and directly on Alzheimer disease (AD) remains to be elucidated. We hypothesized that repeated cold-exposure to transgenic rat model (Tg) of cerebral amyloidosis (AD-like model) could trigger novel cold responsive pathways leading to

major breakthroughs for new frontiers in TH and AD research. Epigenetic regulation of gene transcription would be an appropriate mechanism for cells to flexibly adapt to the environmental modifications. An important enzyme involved in adaptive environmental changes (as cold) is an amine oxidase called lysine specific demethylase 1 (LSD1), that regulates gene transcription. LSD1 is involved in various neural functions, such as learning, memory and the activation of neuroinflammatory responses. However, the role of repeat cold exposures on brain LSD1 function and its impact on neuroinflammatory markers has never been studied. In the present work, 17 months-old non-Tg and Tg rats were daily exposure to ^{4}C chamber for 1h, tested cognitively using the Novel Object Recognition (NOR) test and hippocampal LSD1, IL-1β, nNOS and COX-2 levels were measured. TH controls hippocampal LSD1 and pro-inflammatory cytokines preventing cognitive decline in Tg rats exposed to cold compared to Tg- not exposed ones. Thus, TH holds promise as a therapeutic agent in AD.

Cognition, Behavior, and Memory

P116.-Unsupervised cluster analysis of task solving strategies using an animal model of striatal cholinergic interneurons ablation

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Goal directed tasks (GDT) entail animals behaving according to experimental designs in order to receive a reward or avoid punishment. Many times, however, animals solve mazes through a variety of different individual strategies that may not have been foreseen by the experimenter. We have previously shown that striatal cholinergic interneurons (SCIN) are required to establish solving strategies in spatial navigation tasks. Moreover, our previous results suggest SCIN deletion induces a performance improvement in GDT. Nonetheless, the role of SCIN in other GDT strategies has not been assessed yet. To determine whether SCIN-associated enhancement is explained by a strategy-related change, we conducted an unbiased multivariable analysis of animals' behavior after subjecting control and SCIN ablated mice to a two-alternative free choice operant conditioning task. For that, we studied 19 behavioral variables and used them in an unsupervised cluster analysis. We found that control group was formed by two behavioral clusters that displayed two different strategies. Conversely, lesioned mice constituted a less variable group strongly enriched in a single strategy. These results suggest that: 1) limited behavioral constrains in a GDT could lead to different, but equally effective, solving strategies in control mice. 2) Better performance of lesioned group may be due to a limited competence between strategies, 3) SCIN role in strategy selection may not be limited to navigational tasks.

Cognition, Behavior, and Memory

P117.-Participation of basolateral amygdala complex astrocytes in different stages of a contextual fear memory

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In the last decades, the acknowledge of the fundamental contribution of astrocytes to the synaptic function and plasticity encouraged the study of the role of astrocyte on memory. However, little is known about the role of astrocytes from the basolateral amygdala complex (BLA-C) on the contextual fear conditioning (CFC). Further, if astrocytes play a role in the different stages of memory, i.e. acquisition, consolidation, evocation or

reconsolidation, has not been clarified. Adult wistar male rats were bilaterally canulated in BLA-C and leave for recovery for 10 days. Then they were infused with fluorocitrate (FLC) -an astroyte metabolic inhibitor- or saline at different times respect to the CFC trial in order to target different stages of memory. Memory was evaluated in the same context after conditioning and the percentage of freezing time (fear response) was used as memory index. The group of animals that received FLC before or after CFC showed a significant reduction of freezing during memory testing respective to saline treated controls. When FLC was administered before or after retrieval, the fear index was affected neither during reactivation nor in a further memory test. The results suggest that BLA-C astrocytes play a role in the acquisition/consolidation phases of a CFC memory. However, a similar astrocytic inhibition during or after retrieval did not alter fear memory, suggesting that they are not critically involved on the recall and memory reconsolidation.

Cognition, Behavior, and Memory

P118.-Active and receptive musical training affects emotional and neutral memory in 4- and 5- year-old children

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Musical training has multiple beneficial effects on cognitive development. It could be receptive (the child perceives music and its elements) or active (the child produces music besides perceiving it). One of the cognitive functions that are influenced by musical training is memory. The goal of this study was to evaluate the effect of receptive and active musical training on memory of preschooler's children. They (N = 148) were randomly separated into three groups: receptive or active musical training and a control group without training. Children with training received stimulation for 4 weeks. After that, all children observed 24 images (neutral, positive and negative balance). Memory was tested through two task: free recall and recognition (immediate and deferred). In the immediate free recall the emotional images were better remembered than neutral ones, and for neutral and negative images both musical interventions (active and receptive trainings) remembered more images than control group. In the deferred free recall, emotional images were better remembered than neutral ones, and both musical trainings remembered more neutral, positive and negative images than the control group. Besides, 5-year-old children showed a greater memory than 4-year-old children, and both musical trainings had better recognition scores (immediate and deferred measures) than the control group. These results indicate that musical training can modulate emotional memory.

Cognition, Behavior, and Memory

P119.-Consolidation of human declarative memory: an all-or-nothing process? Preliminary results

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After their acquisition, the new memories go through a lability period in which they become susceptible to the action of either amnesic or facilitators agents. This susceptibility decreases over time and implies a stabilization process known as consolidation. Thus, after learning, the existence of a temporary window is evidenced in which memory is sensitive to interference and, once this period is over, it can no longer be modified. However, spontaneous waves of destabilization have been observed (without the re-exposure to keys linked to learning) in which memory is again sensitive to interference. In the present study we investigate whether declarative memories in humans suffer spontaneous labilizations/re-stabilizations after learning or if they only pass through a single time window, after acquisition, sensitive to interference. Participants learned a list of five pairs of non-sense syllables on day 1. Immediately after, 30 min or 3 hours later they received an interference list that acted as an amnesic agent. They were finally tested on day 3. We also run two control groups that were only trained and tested in one of the tasks. The memory was impaired by the second list only when the interference task was presented immediately after or 3 hours after learning. When the second list was presented 30 min after learning the memory was protected against interference.

Cognition, Behavior, and Memory

P120.-A physically active lifestyle is related to an enhancement in immediate memory for positive valence stimuli

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Physical activity could enhance cognitive functions in a wide age range. The goal of the current study was to evaluate the amount of physical activity people do throughout their daily life and evaluated if this measure was related to emotional memory. Forty-eight young adults completed a self-reported questionnaire referring to the type and quantity of physical activity carried out in a typical week of their lives. Regarding memory, subjects watched a set of pictures with different valence (positive, negative, and neutral), from the International Affective Picture System. After acquisition phase, memory was evaluated through a two-task test: free recall and recognition (immediate and deferred, after one week). We found that participants with a lifestyle more committed to physical-sport activity recalled more positive pictures in the immediate free recall task in comparison to people with moderate and low activity commitment. The high commitment group also showed a high recognition score compared to the other groups. These findings allow us to conclude that a lifestyle committed with activity could improve memory for positive affective stimuli acquired through a visual modality. Physical exercise could be considered an appealing treatment, since it's an easy and low-cost intervention that could be used for people in a wide age range.

Cognition, Behavior, and Memory

P121.-A behavioral-tagging perspective of spaced learning: LTM formation during an inhibitory avoidance task

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Spaced learning is more efficient than massed learning for inducing long-term memories (LTM). Our study examined the temporal demands of this phenomenon and the cellular processes that underlie LTM formation using two weak learning tasks, inhibitory avoidance (wIA) and spatial object recognition (wSOR). A single wIA training session is unable to promote LTM formation when assessed 24 hours later. However, two identical wIA training sessions spaced by different inter-trial intervals led to IA-LTM formation if spacing ranged from 1 hours to 4 hours. This promotion depended on hippocampal protein synthesis and ERKs1/2 activity. We analyzed these results in the context of the "behavioral tagging" hypothesis, which postulates the existence of a tag induced by learning that requires proteins to form LTM. We propose that consecutive sessions of a retraining protocol stimulate the same neural populations, and result in the addition of the intracellular mechanisms triggered by each session. Such an addition would allow reaching the threshold required for protein synthesis and memory consolidation, and would not occur if the neural populations activated by each session differ. In consequence, combining a wIA and a wSOR training session spaced by 4 hours did not result in LTM for either task. Finally, our results suggest that ERKs1/2 kinases are involved in the process of protein synthesis but not in that of tag setting in the IA task.

Cognition, Behavior, and Memory

P122.-Subjective effects and neurophysiological correlates of inhaled consumption of N,N-dimethyltryptamine (DMT) in an urban natural environment.

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Serotonin 5-HT2A receptor agonists are known for their ability to induce profound and transient changes in the user's consciousness. An example of these compounds is the classic serotonergic psychedelic N,N-dimethyltryptamine (DMT) which is frequently consumed both orally —ayahuasca— or via inhalation of free base vapor. In recent years human research using psychotropic substances has been revitalized, yet most of the published experiments were carried out in an isolated experimentation environment. This can modify both the mental state a person brings to the experience, like thoughts, mood and expectations (‘set’) and the physical and social environment ('setting'). The objective of this work is to investigate the consumption of DMT in an urban natural environment; that is, in the context chosen by the users to carry out their experience. Using a minimally invasive experimental design, a series of psychometric scales are administered before and after the experience, during which we record changes in cortical oscillations associated with different stages of the acute effect of consumption, measured with a portable electroencephalograph (EEG). Preliminary results show a reduction in the alpha band spectral power, as reported in previous studies on DMT and other psychedelics, and suggest correlations between personality traits, changes in mood and anxiety scores and the overall effects of the reported experience.

Cognition, Behavior, and Memory

P123.-Molecular mechanisms underlying promotor effect of IGF-1 on the formation of a fear memory trace

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Basolateral amygdala complex (BLA) plays an essential role in the generation of an emotional state caused by an aversive experience. Insulin like growth factor I (IGF-I) could modulate hippocampal circuits modifying cognitive functions, and possibly, the molecular mechanisms involved in some psychopathologies related to traumatic memories. To evaluate the formation of a memory trace through BLA IGF-I gene therapy and synaptic and molecular changes in dorsal hippocampus (HD) and BLA associated with the formation of this memory trace. Adult male Wistar rats were bilaterally infused into BLA with RAd-IGF-I, and RAd-Ds-Red as control. 7 days later we performed a weak fear conditioning protocol (WFCP). Freezing behavior (FB) was assessed at 7th and 14th day. HD synaptic plasticity was assesed through dendritic spine analysis. BLA and HD were obtained for protein analysis. A significantly increase in FB in the RAd-IGF-1 group was observed after 7 daysand 14 days post injection. There was a significant increase in mature spines after RAd-IGF-1 treatment. pERK/ERKt level was increased in BLA in RAd-IGF-1 group at the time WFCP was performed. IGF-I gene therapy induces a significant expression of FB in a WFCP, with a possible promotor effect on the formation of a fear memory trace. This behavioral expression was coincident with changes in HD dendritic plasticity. This effect could be partially attributed to MAPK/ERK pathway activation in BLA

Cognition, Behavior, and Memory

P124.-Pi3k pathway of the 5-HT2A receptor participates in the resolution of memory interference during recovery of object recognition memory in rats.

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Memories are not an exact copy of an event but instead a reconstruction in the brain of that particular event. This fallibility can be altered by certain distortions such as memory interference during the recall. Previous works from our lab showed that the blockade of the medial prefrontal cortex (mPFC) serotonin type 2a receptor (5-HT2AR) affects the resolution of the object-in-context recognition task (OIC). This task presents high level of potential interference suggesting that 5-HT2AR plays a role in the control of this process. However, the molecular pathways within the mPFC underlying this effect remains unclear. Here we tackle this question by performing pharmacological interventions in rats over the β-arrestin2/Pi3k/Src/AKt pathway, one of the most studied pathways activated by the 5-HT2AR, in the mPFC. Our results showed that the infusion of MDL (5-HT2AR antagonist) or LY (Pi3K inhibitor) in the mPFC before the test session impairs the resolution of the OIC. To analyze whether 5-HT2AR and Pi3k are functionally connected we performed a molecular disconnection experiment. If both molecules are involved in the same pathway, then their simultaneous blockade in different structures involved in the task (contralaterally) will generate a deficit. We found that the contralateral infusions of MDL+LY produce a deficit, while when infused ipsilaterally, they did not. These results suggest that Pi3K pathway might underly 5-HT2AR function in the resolution of memory interference.

Cognition, Behavior, and Memory

P125.-Hippocamppal structural plasticity associated to the fear memory destabilization/reconsolidation process

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A consolidated memory can enter a transient labile state when presented with a reminder, requiring a protein synthesis-dependent re-stabilization process termed reconsolidation.It is known that the basolateral amygdala (BLA) and the Dorsal Hippocampus (DH) play a key role in processing emotional information and the contextual representation of fear memories respectively. In the present study, we assessed the modulating role of BLA on the hippocampal structural plasticity associated with the labilization/reconsolidation of a contextual fear memory. We used Ifenprodil (IFEN), a selective NR2B subunit of the NMDA receptor antagonist, infused intra-BLA in male wistar rats, in order to prevent the labilization. Rats were sacrificed 60 minutes and 24 hours after the retrieval session to evaluate the structural plasticity of the CA1 region of DH.
Our results show that rats infused with IFEN present a high number of spines at both 60 minutes and 24 hours post retrieval, while rats infused with saline solution (SAL) show a decrease in dendritic spines 60 minutes after retrieval, consistent with the dynamic changes in dendritic spines observed in our previous work. Altogether, our findings seem to indicate that labilization impairment prevents structural changes in the CA1 region of DH, thus supporting our hypothesis of the modulating role of BLA on the hippocampal structural plasticity and the idea that changes in dendritic spines density are required for a memory to be updated.

Cognition, Behavior, and Memory

P126.-A BEHAVIORAL-TAGGING PERSPECTIVE OF SPACED LEARNING: PERSISTENCE OF CONSOLIDATED MEMORIES CAN BE MODIFIED IN RESPONSE TO RETRAINING

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We assessed the effects of spaced learning on memory persistence using a spatial object recognition (SOR) task. We observed that a weak SOR (wSOR) training session induced short-term but not long-term memory (LTM); whereas a strong SOR (sSOR) training session promoted a 24 h-LTM which did not last 7 days. When animals were exposed to a retraining protocol, in which a sSOR session is followedby a wSOR session 24 h later, we found that LTM did persist for 7 days. This effect depended on protein synthesis and ERKs1/2 activity in the dorsal hippocampus. However, when animals received a test session 24 h after sSOR training the memory persistence was not observed 7 days later. We propose that memory retrieval at the time of retraining is a key factor in this process because the wSOR session performed 7 days after the sSOR training did not yield memory persistence. Also, when we inhibited the protein synthesis induced by a wSOR retraining performed 24 h after a sSOR session, we found thatthe 48h-LTM was not disrupted. This suggests that the memory was not labilized by retraining and thereby a reconsolidation process was not induced. Based on the "behavioral tagging" hypothesis, we postulate that for memory persistence is necessary the setting of a second SOR-learning tag and protein synthesis. Our results suggest that memory retrieval induces these proteins and that a retraining session could retag the same sites previously activated in a more efficient way than a test session.

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P127.-Sex chromosome complement influences communicative behavior in the valproic acid animal model of autism spectrum disorder

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Autism spectrum disorder (ASD) is a group of neurodevelopmental pathologies characterized by persistent deficits in social communication, restricted interest and repetitive behaviours. Given the strong impact of sex on ASD prevalence (4:1 male-to-female ratio), we wonder if the sex chromosome complement modulates the communicative behavior in a valproic acid (VPA)-induced ASD related phenotype in mice.To this end, we used the "four core genotypes" (FCG) mouse model, in which the effect of gonadal sex and sex chromosome complement is dissociated, to determine if sex chromosomes influence the pup ultrasonic vocalizations (USV) induced by maternal-separation.Pregnant mice of the FCG received a single intraperitoneal injection of VPA (500 mg/kg) on gestational day 12.5. During the early postnatal development (PN6-PN12), the USV were recorded in the sound-attenuating chambers for 4 min using a vocalization detector. The total number of USVs emitted in the range 45-100 kHz were analysed by Kruscal Wallis test. The results demonstrated that USVs decreased with development in all groups ($p<0.05$). At PN12, only XY female mice prenatally exposed -VPA showed fewer vocalization than control ($p<0.05$), whereas VPA-treated XY male produced more USVs than VPA-treated XX male pups ($p<0.05$). These results suggest a complex interaction between the genetic background derived from sex chromosomes and the gonadal phenotype that should be explored to contribute to the understanding of ASD.

Cognition, Behavior, and Memory

P128.-Modulation of lateral habenula neuronal activity using optogenetics and an arduino/Bonsai based system to study its role in spatial processing

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The ability to learn and remember is essential for the survival of animals, as it allows to adapt to the changing environment we live in. In the recent past years, the lateral habenula (LHb) has gained attention in the field of neurobiology and systems neuroscience, as it is a key structure in motivation signaling receiving inputs from the basal ganglia and limbic structures and projecting to regions such as the ventral tegmental area and the rostromedial tegmental nucleus. Moreover, it is functionally related to the hippocampus, albeit not directly connected. In fact, there is evidence showing LHb is necessary for spatial processing. In this scenario, our goal is to study how the LHb is involved in the processing of spatial information, to assess in which mnesic processes it is necessary, and ultimately how it functionally interacts with the hippocampus for the coding and reprocessing of spatial information. Here, we present the project by which we plan to address our goals and will show the

progress of some experiments modulating the LHb using optogenetics together with an arduino/Bonsai based system to deliver blue light depending on the location of the rats, both in a spatial dependent task and a rewarded task.

Cognition, Behavior, and Memory

P129.-Focal musical interventions to improve memory consolidation

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Memory, as a cognitive function that allows us to store learned information, has a series of phases for the formation of the mnemonic trace, which include acquisition and encoding, consolidation, storage and evocation of the information. Different treatments that modulate the process of memory formation have been identified through interventions in some of the mentioned phases. Musical activities have been tested as modulator´s treatments in some types of episodic memory, such as emotional memory. The aim of this study was to investigate the effect of a focal music intervention on visual and verbal memory. In this study participated 237 young adults and 186 older adults (musicians and non-musicians), randomly assigned to the different experimental treatments. We evaluated visual memory using the Rey Complex Figure and verbal memory using the Rey Auditory Verbal Learning Test. After acquisition of visual or verbal information, groups were exposed to one of the experimental interventions (music improvisation or rhythmic reproduction) or to a control condition (rest) for 3 min. Then we evaluated memory through two tasks (free recall and recognition), by means of immediate and deferred measures (after a week).The main finding of this study indicated that musical improvisation improves delayed free recall for visual and verbal information in both groups of participants. On the other hand, participants who had musical knowledge had a better performance than non-musicians.

Cognition, Behavior, and Memory

P130.-Memory impairment induced by different types of prolonged stress is dependent on the phase of the estrous cycle in female rats

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A growing body of evidence demonstrates that estrogen and corticosterone (CORT) impact on cognition and emotion. On the one hand, ovarian hormones may have beneficial effects on several neurophysiological processes, including memory. On the other hand, chronic exposure to stressful conditions has negative effects on brain structures related to learning andmemory. In the present study, we used the plus-maze discriminative avoidance task (PMDAT) to evaluate the influence of endogenous variations of sex hormones and exposure to different types of prolonged stressors on learning, memory, anxiety-like behavior and locomotion. Female

Wistar rats were submitted to seven consecutive days of restraint stress (4h/day), overcrowding (18h/day) or social isolation (18h/day) and tested in different phases of the estrous cycle. The main results showed that: (1) neither stress conditions nor estrous cycle modified PMDAT acquisition; (2) restraint stress and social isolation induced memory impairments; (3) this impairment was observed particularly in females in metestrus/diestrus; (4) stressed females in estrus displayed less riskassessment behavior, suggesting reduced anxiety-like behavior; (5) restraint stress and social isolation, but not overcrowding, elevated corticosterone levels. Taken together, our findings suggest that the phase of the estrous cycle is an important modulatory factor of the cognitive processing disrupted by stress in female rats.

Cognition, Behavior, and Memory

P131.-The classic mutant dunce1 is amnesic for olfactory conditioning and hypermnesic for context recognition

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Habituation is the most basic form of learning. It describes the decrease of a behavioral response to a repeated non-threatening sensory stimulus. The mechanisms of habituation are considered to be a prerequisite for other forms of learning. Suggestively, genes involved in intellectual disability are required for reflexive habituation. However, very little is known about habituation in motivated behaviors. Here we established a learning paradigm of context recognition in Drosophila, in which habituation and sensitization were predominant behaviors during learning and memory, respectively. We characterized the behavioral response of flies subjected to distinct protocols composed by one or two training trials with different length and different inter-trial intervals. Protocols with longer training trials led to an increased memory. The dunce (dnc) PDE restricts the level of cAMP at the presynapse, a function that is widely accepted to cause deficits in short-lived memory performances once deregulated in dnc1 (PDE loss-of-function) mutants. Surprisingly, dnc1 animals showed an increased short-term memory to the context, contrary to what had been shown in olfactory conditioning. Consistently, during training dnc1 showed a stronger habituation than wild-type flies, suggesting a better learning. These results show that the real nature of some classic mutants is more complex than we previously thought, and it might depend on the specific brain function involved.

Cognition, Behavior, and Memory

P132.-Spatial auditory representations by blind and sighted humans in the peripersonal space

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Compared to sighted listeners, blind listeners tend to underestimate their egocentric distance judgments for sound sources located beyond the peripersonal space (the portion of space near the body where individuals can interact with objects), in the absence of additional sensory information. It has been hypothesized that this effect is the consequence of the lack of visual information about the source position. Visual information is thought to be used by sighted listeners throughout their lives to calibrate the auditory spatial information provided by the

source and, therefore, build an accurate representation of the auditory space. However, in the absence of visual information, humans could use proprioceptive and tactile information as alternative sources of information when the auditory target is within hand reach. In order to test this hypothesis, we collected both auditory distance and auditory reachability judgments for blind and sighted listeners. Sound sources covered the range from 20 cm to 260 cm. We studied the group differences in distance estimations obtained by reaching (direct action) in the peripersonal space and verbal reports in both the peripersonal and extrapersonal space. We found two sub-populations among blind subjects, one that supports this hypothesis and another one that seems to be unable to discriminate auditory distance for the whole range of distances within the peripersonal space.

Cognition, Behavior, and Memory

P133.-Role of Serotonergic Alterations during embriogenesis in the development of problematic behavior

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Serotonin (5-HT) is a monoamine neuromodulator that is involved in the regulation of numerous physiological and behavioral functions including mood and anxiety related behaviors. 5-HT is also involved in refining the formation of brain circuits during sensitive developmental periods. It is not surprising, though, that 5-HT plays an important role in the development of psyquiatric disorders such as social deficits, anxiety, depression and addiction problems. It is known that anxiety disorders have developmental origins and that 5-HT is implicated in these processes. Disruption in 5-HT system during sensitive periods of development results in long term consequences. Anxiety disorders are also comorbid with another disorders, such as alcohol abuse and dependence. Therefore, alterations in 5-HT system may be also related with problematic use of alcohol. In order to analyze the effects of 5-HT alterations during embryogenesis, we treated c57 mice with a 5-HT synthesis inhibitor (PCPA; 4-Chloro-DL-phenylalanine methyl ester hydrochloride) during E14-17 and conducted a behavioral screening for anxiety, social preference and alcohol-induced anxiolysis. We found that animals that were depleted of 5-HT during embryogenesis showed social anxiety behaviors and are more sensitive to the anxiolytic effect of alcohol.

Cognition, Behavior, and Memory

P134.-Stress affects predictive learning in a contextual fear memory

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A growing amount of evidence has shown that consolidated fear memories can enter a transient labile phase under certain conditions. Prediction error, defined as the discrepancy between an expectation and what the organism experiences is crucial for triggering the destabilization/reconsolidation process. On the other hand, stress facilitates the formation of a fear memory resistant to destabilization. However, the role of stress on prediction error has not been investigated. The goal of the present study was to investigate the effect of stress

on the temporal prediction error in contextual fear conditioning in rats.The results suggest that stress affects the temporal prediction error related to the unconditioned stimulus arrival. As expected, Midazolam (MDZ) interferes with memory reconsolidation in control rats. In contrast, stressed rats displayed a fear memory resistant to the MDZ's disruptive effect. Given that d-cycloserine (DCS, NMDA receptor partial agonist) facilitates memory destabilization, we next investigated the effect of pre-reactivation DCS combined with post-reactivation MDZ on fear memory reconsolidation in stressed rats.DCS restored vulnerability to MDZ disruptive effect but fail to recover the temporal prediction error about the arrival of the unconditioned stimulus. This effect was not observed in DCS stressed rats injected with vehicle. Fear learning under highly arousing events limits the occurrence of temporal prediction error during reactivation.

Cognition, Behavior, and Memory

P135.-Altered gene expression in medial prefrontal cortex correlates with social cognition deficits derived from perinatal malnutrition in a mouse model

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Early life adversities such as perinatal malnutrition can modulate neuronal plasticity contributing to neurophysiologic and behavioral alterations. However, mechanisms mediating these effects are not completely known. The aim of this work was to evaluate the impact of perinatal malnutrition on social cognition. We used CF1 dams fed with normal (NP, casein 20%) or low protein diet (LP, casein 8%) during pregnancy and lactation. Offspring were analyzed at PD56. Preclinical PET analysis showed an altered activity in the prefrontal cortex (mPFC) of LP mice suggesting a deficit in the function of this brain's region. The mPFC is involved in the regulation of social cognition. We found that contextual recognition memory, social interaction and social memory were impaired in LP mice. Besides, LP mice exhibited an increased dominance hierarchy. To investigate the potential contribution of E/I imbalance in the mPFC to these behaviors, we evaluate the expression of genes involved in Gabaergic and Glutamatergic transmission. LP mice expressed higher levels of Gria1 and Vglut1 than their NP counterparts. In addition, expression of HDAC2, 5, 7, 10 and 11 were decreased in LP mice. Immunoblot analysis revealed global changes in repressive histone marks H3K9me3 and H3K27me3 and activator mark H3K4me3. We propose that alteration of epigenetic mechanisms during brain development caused by perinatal malnutrition could lead to altered E/I balance and subsequent deficits in the social domain.

Cognition, Behavior, and Memory

P136.-Deconstructing the spatial problem-solving of Tower of London: Analysis of task difficulty through the performance of preschool children

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The Tower of London (TOL) task has been frequently used to assess planning processes. Task difficulty has been associated with children´s performance, and it concern in several characteristics which has been associated to the problem space. In the present work, 252 children from 3 to 5 years of age from Buenos Aires were assessed

with TOL. A logistic regression model was implemented in order to identify task characteristics factors (i.e., initial and final spatial arrangement, type of first movement and arrival options) associated with the children´s performances. Based on it, different resolution profiles (i.e., below, above and equal the median) based on the H index (which consider the own performance throughout the task and average performance of the sample) were identified. The total variance was 0.5% (R2 = .005) and results indicated that trials whose final spatial arrangement tend to be plane-shaped (B=.04; p<.001), most difficult first movements (B=.16; p<.001) and fewer arrival options (B=-.12; p<.001) were associated with most effective performance profiles. These findings address the importance of considering the problem space to design assessments aimed at identifying individual differences.

Cognition, Behavior, and Memory

P137.-Long term memory of a spatial learning task in the crab Neohelice granulata
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In the wild, animals are able to recognize and remember specific locations related to food source and/or possible predation. In order to do so, long-term memories are formed, associating spatial cues with appetitive or aversive stimuli. Therefore, further understanding of spatial memories isa relevant question for behavioral neuroscience. With this in mind, we set to develop a novel paradigm for crab Neohelice granulata which is suitable for appetitive spatial conditioning. During the training session, animals are placed in a circular arena, which consists of plain white floor and walls, except for one striped quadrant. After habituation to the training context, crabs are appetitively conditioned through placing palatable reinforcement in the striped section of the arena. When tested, 24 hours after training, trained animals spend more time in the striped section of the arena, relative to the plain white one, compared to control animals. Importantly, we defined the parametric conditions for this novel paradigm (training session duration, unconditioned stimulus intensity, etc), as well as characterizing the resulting long-term memory (protein synthesis and NMDA-R dependance). In addition, we studied how the animal's motivational state can modify its unconditioned behavior. Overall, this work provides evidence to establish the basis for a novel spatial paradigm in crab Neohelice granulata.

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P138.-Memory updating during reconsolidation relays on a behavioral tagging process
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We have recently shown that the reconsolidation of different memories occurs via a behavioral tagging (BT) process. In other words, to re-stabilize a memory upon its reactivation two parallel and complementary processes must occur: the setting of reconsolidation tag and the synthesis of new proteins (PRPs). Here, using the spatial object recognition (SOR) task in rats, we investigated how the BT process regulates the addition of new information to the trace. Our results show that the inhibition of the protein kinase A (PKA) and the

extracellular regulated kinases 1/2 (ERK1/2) upon memory reactivation impaired its reconsolidation, unveiling those pathways as mechanisms related to the setting of the tag and the synthesis of PRPs respectively. In addition, we studied the role of the dopaminergic and adrenergic systems. We observed that the β-adrenergic and the D1/D5-dopaminergic receptors of the hippocampus are specifically required to induce the synthesis of PRPs necessary to grant the reconsolidation process and add new information to the trace. Moreover, by combining SOR memory reactivation with the exploration to multiple novel arenas at different time points, we observed that each exposure, capable of providing further PRPs, induced a better long-term memory. In summary, our results show that the BT underlays the addition of new information to a memory trace during memory reconsolidation and they start to unveil the mechanisms underlying the process.

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P139.-Hippocampal Sharp-Wave Ripples and episodic memory onset along development

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Episodic memory relies on the ability of the hippocampus to process spatial information. This type of memory emerges late on postnatal lifetime, in correlation with hippocampal development. When this memory is build-up by using external/distal environmental cues is known as allocentric memory and, it is the latest form of episodic memory to emerge. Recently, it has been shown that allocentric memory is observed since postnatal day 18 (P18), but it is not fully developed until P38, when it reaches the adult-like form. However, it has been proposed that early reinforcement by allocentric task training could accelerate its adult-like expression.

Although the mechanisms of memory formation remain unclear, research has pointed out sleep as a memory promoter and oscillatory electrical rhythms during sleep, such as cortical slow waves (< 1Hz), and hippocampal sharp-wave ripples (SWRs,100-250 Hz) as correlates of memory consolidation. With the aim to determine whether allocentric reinforcement could anticipate the maturation of episodic memory in parallel with changes in oscillatory activity, we performed an object-place task with or without reinforcement and in vivo LFP recordings, throughout animal development, in the somatosensory and hippocampal cortices. Our results show that allocentric memory emerges around P32 (n=11, p=0.042), independently of early reinforcement and, changes in the power and density of sleep SWRs accompany the emergence of memory consolidation.

Cognition, Behavior, and Memory

P140.-Medial prefrontal cortex (mPFC) encoding of contextual information in a mice model of schizophrenia

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The medial prefrontal cortex (mPFC) is involved in various forms of cognition that depend on contextual information to guide goal directed behaviors. To do so, the mPFC provides a global representation of the spatial context, incorporating emotional elements to form a complex contextual representation. This representation can be dynamically rearranged depending on cognitive loads and behavioral demands. Altered mPFC function has been associated to the pathophysiology of schizophrenia (SZ) and may be subjacent to the profound

cognitive impairments displayed by these patients. Little is known about how mPFC encodes contextual representations and how these representations are altered in SZ. Here, we recorded mPFC neurons activity in a validated SZ-mouse model (NMDA receptors ablated in corticolimbic PV+ interneurons, KO) and control mice while performing exploratory tasks under different degrees of cognitive and emotional load. We observed differences between control and KO regarding their contextual representation (including firing rate and number of engaged units) while analyzing activity of putative pyramidal mPFC neurons. The differences between control and KO depend on the task's cognitive load and are exacerbated when salient social stimuli are incorporated into the environment. These findings can help us understand how the mPFC integrates relevant contextual information and regulates exploratory behaviors in normal and pathological conditions.

Cognition, Behavior, and Memory

P141.-High-fat diet consumption for a short period sensitizes SNC to mild immune challenge and impaired contextual fear memory

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Hippocampal neuroinflammation normally increases with age, but risk of neuroinflammation, cognitive impairment, and neurodegenerative diseases is exacerbated by chronic consumption of high fat diets (HFD) in young and adults.Also, consumption of HFD for a short time period has been shown to sensitize the inflammatory response to a subsequent immune challenge. Moreover, neuroinflammation and astrocytes activation and proliferation represent a common link between neurodegenerative diseases and metabolic related disorders. α-MSH is a potent anti-inflammatory peptide and previous results of our group indicated that α-MSH could reverse the effect of the neuroinflammation induce by IL-1β on memory consolidation and reconsolidation. We explored whether 5 days consumption of HFD (60% of cal from fat) can trigger a neuroinflammatory response in rats that received a mild immune challenge (LPS), leading to cognitive deficits.
Ingestion of a HFD for 5 days did not impair fear contextual memory. However, the intraperitoneal injection of LPS impaired memory consolidation in HFD rats. The treatment with α-MSH in dorsal hippocampus reversed the effect of HFD+LPS administration in contextual fear memory. We are also studying astrocytes proliferation and activation. In summary, our present results indicate that HFD consumption for a short period sensitizes SNC to mild immune challenge and produces an impairment in the contextual fear memory that could be related to changes in glial cells.

Cognition, Behavior, and Memory

P142.-Is sleep involved in the consolidation and integration of new words? A refractory temporal lobe epilepsy study

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New memories are reactivated during sleep reinforcing cortico-cortical connections favoring memory consolidation. There are contradictory results concerning the role of sleep in new word consolidation, some studies reveal a fast integration independent of sleep while others show sleep-dependent integration of new words. Patients suffering Temporal Lobe Epilepsy (TLE) often show deficits in consolidation of declarative memories. It has been shown that TLE patients have a temporal coupling desynchronization between hippocampal ripples and cortical slow oscillations, a mechanism implicated in off-line memory consolidation. Using a word learning task we evaluated the role of sleep in consolidation and integration in patients with refractory TLE. Participants performed a word learning task and slept for 8h while a polysomnography was performed, or they remain awake for 8h. Memory retention was tested after that period. Our results showed that the Wake group had a better performance than the Sleep group. Furthermore, we observed positive correlations between time spent in Slow Wave Sleep (SWS), power density for slow waves (0.5-1 Hz), delta (1-4 Hz), theta waves (4-8 Hz) in S2 and SWS and memory performance. Thus, while TLE patients showed an impaired consolidation during sleep compared to the wake group, the more time spent in SWS sleep and the more power density of slow wave activity in No-REM sleep, the better the memory performance.

Cognition, Behavior, and Memory

P143.-Validation of Neurolinguistic protocols on a portable low-cost EEG equipment

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Electroencephalography (EEG) is a non-invasive neuroimaging method in which cortical electrical activity is recorded with great temporal precision using electrodes placed on the scalp. Experiments with EEG have been critical in the study of language processing, identifying stereotyped responses associated with semantic (N400), or grammatical (LAN / P600) manipulations, among others. These studies are usually carried out in controlled environments within the laboratory, using expensive and complex setup. However, low-cost portable devices have recently appeared. These new advances allowed for experiments to be performed in more ecological environments (e.g. schools or low-income hospitals) opening up a wide range of possible applications. In the present work, we used two classic psycholinguistics tasks to develop a protocol for using a low-cost and high-portability EEG device (EMOTIV EPOC+) to evaluate different linguistic capabilities. We observed significant differences between correctly formulated sentences and sentences with semantic inconsistencies. These differences in brain potentials were observed in the expected latency, but not in the expected polarity. We hypothesized that these discrepancies might be due to the electrodes layout. This study shows promising results for using this type of device outside the laboratory, allowing to study neurocognitive aspects in more natural environments and in massive scale.

Cognition, Behavior, and Memory

P144.-Two different memory traces are formed when honey bees associate odors with appetitive and aversive stimuli

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Animals must be able to extract information from situations in which aversive and appetitive consequences appear intermingled. How this information is stored and retrieved to ensure coherent and adaptive behaviour is an important question in neurobiology. Honey bees represent a great model to answer this question since there are in this species well characterized behavioural paradigms to study appetitive and aversive learning and memory. In the appetitive version, an odor is associated with sucrose and animals extend the proboscis upon stimulation with the conditioned odor. In the aversive version, odor is presented with a salty or bitter solution and animals withdrawal the proboscis upon stimulation with the odor. In the present study we combined these two paradigms in a series of experiments aimed at evaluating in which extent the two forms of memories are independently established or interact when appetitive and aversive stimuli take part of the same training protocol. We found that bees were able to recognize appetitive and aversive learned odors embedded in complex mixtures. In addition, bees could establish independent appetitive and aversive memories acquired during the same training session. Finally, when bees were challenged in a test session in which the appetitive and the aversive odors were mixed, they could behave according to the appetitive or the aversive odor depending on their motivational state.

Cognition, Behavior, and Memory

P145.-Updating the meaning of a word: memory reactivation boosts integration into an existing memory trace

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Words are extremely malleable memories, subject to updating and modification. However, the mechanisms that allow this plasticity remain unclear. In two different studies we analyzed the contribution of memory reactivation to the enhancement (Study 1) and updating (Study 2) of a word's meaning.Native speakers of Spanish (19-35 years) learned low-frequency words within their language (e.g. 'Ergotina') and their corresponding definitions ('Remedy for haemorrhages'). The following day, Reactivation groups were exposed to a reminder, consisting of the list of words they learnt the previous day, but without their definitions (thus generating a prediction error). No Reactivation groups, on the other hand, did not receive a reminder. In Study 1 (N=34), memory retention was evaluated 7 days after training using a semantic judgment task. In Study 2 (N=73), participants learned a new information for each of the words' definitions (e.g. 'ergotina is extracted from a rye fungus'). Retention for the updated word's memory was evaluated 48 h after training using a cued-recall test. Results of Study 1 show a significant enhancement of semantic recognition speed in the Reactivation group.Regarding memory updating, Study 2 reveals a significant enhancement of the new info memory that increases according to the reactivation strength of each word. Taking into account both results, memory reactivation might be one of the mechanisms that allow the rebuilding of the mental lexicon.

Cognition, Behavior, and Memory

P146.-The role of sleep in word learning in a case report of refractory epilepsy

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Patients suffering Temporal Lobe Epilepsy (TLE) often show deficits in consolidation of declarative memories. Interictal Epileptoform Discharges (IEDs) were proposed as a possible factor of cognitive impairment. It was previously shown using intracranial recordings that hippocampal IEDs damage memory consolidation but not its acquisition. Here, we analyze a case report exhibiting right hippocampal IEDs during sleep and we compared it to a group of TLE patients. All Participants learned a list of novel words before sleeping for 8 h while a polysomnography was performed. After being awaken the memory was tested. In contrast to our expectations, the case report showed better off-line consolidation for new words compared to the TLE group. Moreover, in the TLE group the power density in slow wave activity (slow oscillations: 0.5-1 Hz, delta: 1-4Hz and theta: 4-8Hz) in No-REM sleep positively correlated with memory performance. The results are discussed in terms of the Off-line Active System Consolidation Theory and the possible role of the left hippocampus on memory reactivation during sleep.

Cognition, Behavior, and Memory

P147.-Early behavioral phenotypes in a mouse model of tauopathy

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Tauopathies are neurodegenerative disorders characterized by the abnormal metabolism of the protein tau, which accumulates as insoluble neuronal deposits. The primary Tau transcript generates two isoforms present in equal amounts in the normal adult brain. Several tauopathies have been associated with defects in the alternative splicing of the primary Tau transcript generating imbalances in the tau isoforms. Our working hypothesis assumes that in such tauopathies the presence of abnormal Tau isoforms leads functional deficits prior to the formation of tau aggregates. Therefore, the aim of this project is to describe the early phenotypes of a mouse model with abnormal tau isoforms content, the htau model. Htau mice develop severe tau pathology and neurodegeneration from 9 months old. We analyzed olfactory capacity and performed a battery of tests to detect anxiety, behavioral inhibition and cognitive impairment, in 6 months old htau mice. The innate response to odors and reward motivated odor discrimination tests indicate that htau mice did not show impairments in olfactory function. We performed the nesting test, marble burial test and the elevated plus, which might be affected in animals with anxiety phenotypes. Results indicate a significant tendency of htau mice towards the open arms in the elevated plus maze and a deficit in the marble burial task. Finally, the novel object recognition test was performed, showing that htau mice have cognitive impairments.

Cognition, Behavior, and Memory

P148.-The role of sleep on reinforcement of consolidated memories: Preliminar results

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Consolidated memories may be reactivated by a reminder of the original memory; followed by a process of re-stabilization known as reconsolidation. We have previously observed that the presentation of two consecutive reminders reinforces memory re-stabilization. On the other hand, we demonstrated that 90-min nap after memory reactivation shortened the time window of reconsolidation being S2 and SWS EEG slow-wave activity involved in this process. However, it is not clear whether it stabilizes the trace protecting the memory against interferences or if it strengthens the labilized memory making it more difficult for it to be disrupted. Here, we are going to discuss preliminary data disentangling this matter. For that, participants learned a list of 5 syllable pairs on Day 1, they receive one or two consecutive reminders on Day 2 or one reminder followed by a 90-min nap followed or not by an interference task and they were tested on Day 3.

Cognition, Behavior, and Memory

P149.-Executing a spatial task increases neuronal progenitor proliferation in discrete pallial regions of adult zebrafish

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The teleost's pallium is known to be related to cognitive abilities like learning, memory and emotion. This region, as well as the entire encephalon, is subjected to constant remodelling by the addition of new-born neurons. In particular, the lateral pallium (LP) is proposed to be involved in processing spatial information, and has been postulated to be an homolog of the mammalian hippocampus. However, little is known about the impact of behaviour on neural circuit plasticity. In this work, we studied the involvement of zebrafish's pallium in a spatial constancy task by analyzing neural activation and cell proliferation along the rostro-caudal axis. We described the c-fos expression profile and found selective activation of the medio-caudal LP in trained individuals when compared to learning controls. Regarding cell proliferation, we also observed that trained fish increases PCNA expression in two restricted pallial sub-regions: rostral medial pallium (MP) and caudal LP. In sum, we successfully assessed zebrafish cognitive ability in a spatial constancy task, and found an activity-dependent increase in proliferation of neuronal progenitors located in discrete pallial sub-regions. It remains to be explored whether this proliferation raise results in an increase in adult neurogenesis in telencephalic pallium.

Cognition, Behavior, and Memory

P150.-Molecular mechanisms in the DG and CA3 regulate the balance between differentiation and generalization during retrieval in a cue-degraded context

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Because our environment is permanently evolving, it is crucial for episodic memory to remember our previous experiences despite environmental changes. Computational models have suggested the existence of a pattern completion process by which networks could retrieve entire memories from partial or degraded cues. The CA3 region of the hippocampus was proposed to mediate this computation by the plastic enhancement of the recurrent collateral connections of CA3 neurons that were active during learning. In this work, we manipulated the amount of cues available during retrieval (test phase) in a spontaneous object recognition task to investigate the function of CA3 NMDA-receptors (NMDAR) for pattern completion. We show that pharmacological intervention of hippocampal CA3 NMDAR receptors impairs retrieval of the object location memory only when cues are degraded, while similar manipulations in the dentate gyrus have no effect. Moreover, while the context alone is enough o guide retrieval of the object memory under partial cues, antagonists of NMDAR in the test phase prevent this retrieval. These findings suggest that NMDAR in CA3 are necessary for the retrieval of spatial memories when the amount of environmental information is reduced, and that plastic changes in the dentate gyrus and CA3 are important to define if behavioral pattern separation or pattern completion occurs when exposed to a modified context.

Cognition, Behavior, and Memory

P151.-Burn-out?

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Workers make up half the world's population and are the largest contributors to economic and social development. Their health is conditioned not only by hazards in the workplace, but also by social and individual factors and by access to health services. On the other hand, work-related stress constitutes an increasing risk to the health of Western societies, consequently, mental health of workers is considered crucial both for the individual and for society. A crucial occupational phenomenon is burnout. Methods: a multioccupational sample of 300 workers was analyzed. Burnout and engagement levels were analyzed using self-report instruments. In addition, each participant was asked to provide three saliva samples in the morning. (T0 , T30 and T45). Cortisol levels were determined by ECLIA. Results: Four groups of workers were described by cluster analysis.AUCg values were calculated for each group, showing differences in cortisol levels between groups. Conclusion: In this study we have been able to describe 4 possible stages from engagement to burnout, along with cortisol variations to each stage.

Cognition, Behavior, and Memory

P152.-Postgraduate students and stress

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Emotional disorders (ED) have a high prevalence worldwide and have been related to chronic stress. In addition, graduate students go through a work environment conducive to triggering this type of stress. To verify the association between burnout and ED; to compare the levels of chronic stress, anxiety and depression between graduate students and a control group. Finally, the relationship of these variables with salivary cortisol (C) levels will be studied. Sample 86 Argentinian workers. Of the total sample, 56 were graduate students and the rest were workers from private companies. Instruments were applied to measure chronic stress (MBI-GS), generalized anxiety (GAD 7) and depression (PHQ 9) and salivary (C) was analyzed by ECLIA at 3 different times. The results show a moderate to strong correlation between the central dimensions of the burnout and the ED. Specifically, exhaustion correlated strongly and positively with both Anxiety (r=.64, p<.01) and Depression (r=.63, p<.01). Cynicism presented moderate and positive correlations with Anxiety (r=.42, p<.01) and Depression (r=.37, p<.01). Graduate students presented higher levels of Exhaustion, Cynicism, Anxiety and Depression. In sum, the results show that burnout, anxiety and depression are more prevalent in the graduate student population.

Cognition, Behavior, and Memory

P153.-Oscillatory brain activity induced by target memory reactivations during slow wave sleep: Preliminary results

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Consolidated memories can be reactivated by a reminder of the original memory; followed by a process of re-stabilization known as reconsolidation.Sleep is known to support the consolidation of newly encoded memories and we have previously demonstrated that sleep has a beneficial effect on reconsolidation and that the slow wave activity (0.5-8Hz) during No-REM sleep correlates with memory re-stabilization.Several studies, induced reactivations during the sleep period after acquision, by presenting cues previously associated with the learned material, showing an enhanced performance after reactivations. However, only one study in mice provides the first evidence the consolidated memories can be also strengthened by presenting cues during sleep and that this process is mediated by labilization/restabilization mechanisms. So, here we test if a human consolidated declarative memory can be modified during Slow Wave Sleep by presenting auditory cues associated to the learned material. For that, participants were trained on day 1 in a sound-word paradigm. On day 2 day slept for 90 minutes and they received or not, during Slow Wave Sleep, reminders of the learned associations. 30 min after being awaken they were tested. Participants that received reminders during (SWS) showed a better performance than the no reactivated group. Reactivation during SWS were associated to an increase in theta and spindle power during syllable-cue presentation.

Cognition, Behavior, and Memory

P154.-Perinatal and adolescent protein malnutrition have different effects on cognition in adult mice

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Exposure to environmental adversities, whether it occurs during the perinatal period, childhood, adolescence or adulthood, has an impact on developing brain. The effects of these adversities on brain and behavior arise as a function of the timing and duration of the exposure and its co-occurrence with the development of specific regions (life cycle model of stress). Here we explore the behavioral phenotypes derived from two nutritional stress paradigms: a low-protein perinatal diet during gestation and lactation (E0-P21), and a low-protein diet during adolescence (p25-P56). Locomotor and exploratory activity, recognition memory and aversive memory were measured in CF-1 8-week-old mice subjected to perinatal (LP-P) or adolescent (LP-A) malnutrition, and their respective controls (NP-P and NP-A). We found a reduced exploration in LP-P and LP-A mice compared to controls, although locomotor activity was not altered. Recognition memory was impaired only in LP-P mice. Interestingly, aversive memory was not altered in LP-P mice but resulted to be enhanced in LP-A mice. Considering the stress-inoculation theory, we hypothesized that protein malnutrition during adolescence represents a challenging but still moderate stressful environment, which promotes active coping in face of later adversity. In conclusion, our results indicate that while perinatal malnutrition impairs recognition memory, adolescent malnutrition enhances aversive memory showing dissimilar adaptative responses.

Cognition, Behavior, and Memory

P155.-Spatial and non-spatial memory performance during aging: strategies for memory enhancement
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Changes in memory are one of the main symptoms ofnormal aging. Pattern separation, a process by which the brain stores similar experiences as different memories, may become less efficient as aging occurs, this may be due to changes in subregions of the Hippocampus that are crucial for spatial memories.The Perirhinal Cortex is also involved in differentiation of object-related memories, but the contribution of non-spatial overlapping memory discrimination to normal age-related memory impairment is little known. Different strategies may stimulate specific brain regions and improve memory skills. Cognitive training uses certain kinds of training schedules to stimulate specific brain skills whereas environmental enrichment relies on the physical and social surroundings. The aim of this work is to compare performances of young and aged animals in spatial and non-spatial memory tasks and to determine if different strategies enhance pattern separation in the object and spatial-related domains. Here we reveal a domain-dependent impairment in behavioral pattern separation with aging, where spatial memories seem to be affected independently of the similarity of the experiences whereas object memories are only affected when the stimuli are similar, but not when they can be easily discriminated.We're currently investigating whether cognitive training and environmental enrichment improve spatial and non-spatial memories in young and old animals.

Cognition, Behavior, and Memory

P156.-Single neuron recordings in epileptic patients candidate to respective surgery

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It is well known that the medial temporal lobe has a crucial role in the creation, consolidation and recall of declarative memory. The formation f a new concept is strongly associated to the meaning we give to the sensory information we perceive, and it involves a process of ignoring details to focus on relevant features. In the last decades, it was demonstrated that the hippocampus and the amygdala play a crucial role in these processes. Neurons in this location are involved in the processes of creating and storing different concepts. Intracranial EEG recordings are sometimes needed in patients with pharmacoresistant epilepsy, who candidates to surgery to define the epileptogenic zone. These cases give us the unique opportunity of recording the activity of single neurons (SN) in human subjects. In this poster we describe the technology involved in performing these recordings and show responses to picture presentations, which have been postulated to be involved in declarative memory processes.

Cognition, Behavior, and Memory

P157.-Long-term memory induced by two training trials in the crab *Neohelice granulata*

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Historically, context-specific long term memory (LTM) in the crab Neohelice granulata was established after 15 training trials using aversive stimuli presentation with an intertrial interval (ITI) of 3 minutes. Based on previous studies in Aplysia, we designed a new training protocol of 2-trials (ITI: 45min) that shows LTM expression at least 96h afterwards (2t-LTM). We found that 2t-LTM is dependent on the ITI (45 min, but not 3 or 60 min ITI, allows 24h-memory formation), is context-specific and is disrupted by protein synthesis inhibitors both during consolidation and reconsolidation. Moreover, a MEK1/2 (mitogen-activated extracellular signal-regulated kinase 1/2, ERK1/2 kinase) inhibitor administered between both training trials selectively impaired 2t-LTM when given 15 or 22.5 min after the first one. The underlying hypothesis is that the first trial induces a specific molecular context in the neurons involved in the trace, mediated by the activation of the ERK/MAPK pathway. Upon second trial presentation, LTM formation is triggered specifically in the 45min-ITI condition. Here, we show that 2t-LTM parametrically resembles other conditioning protocols and represents an attractive model for studying individual trial input and ITI contribution to the activation of putative molecular pathways involved in memory formation.

Cognition, Behavior, and Memory

P158.-Over eight hundred cannabis strains characterized by the relationship between their subjective effects, perceptual profiles, and chemical compositions

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Commercial cannabis strains have multiplied in recent years due to regional changes in legislation for medicinal and recreational use. The lack of standardized systems to label plants and seeds hinders the consistent identification of strains with elicited psychoactive effects. We analyzed a publicly available dataset where users reported experiences with different strains, including effects and flavor tags. Metrics of strain similarity based on these tags allowed machine learning classification into three major clusters associated with species (sativa, indica, and hybrids). Synergy between terpene and cannabinoid content was suggested by significant correlations between psychoactive effects and flavor tags. The tags were validated by the application of Latent Semantic Analysis (LSA) to unstructured reviews, also providing breed-specific topics consistent with their medicinal and subjective effects. While cannabinoid content was variable even within individual strains, terpene profiles matched perceptual characterizations made by users and could be used to predict psychoactive effects. Our work represents the first data-driven synthesis of self-reported and chemical information on a large number of cannabis strains. Since terpene content is robustly inherited and less influenced by environmental factors, flavor perception could represent a reliable marker for the prediction of psychoactive effects of cannabis.

Cognition, Behavior, and Memory

P159.-A highly demanding working memory task is able to interfere the reconsolidation of a threat memory

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Consolidated memories can be reactivated into a labile state by the presentation of a reminder. The reactivation of the memory trace is followed by a process of re-stabilization known as reconsolidation. In most of reconsolidation studies, a second task, with similar characteristics to those of the target memory, is used as an amnesic agent. Anxiety manifest as a persistent and generalized defensive system, activated when predicted aversive events are perceived as a threat and uncertain. In laboratory, threat conditioning has been taken as the paradigm for assessing fear memories and anxiety related disorders. In the framework of the reconsolidation the idea that this process would allow to modify this type of maladaptive memories has been proposed.Here we aim to interfere the re-stabilization of an implicit aversive memory using a working memory task, which aimed to overload this transient memory system. To reach such goal, we design a 3 day protocol, and compared a trained threat conditioning group, that 24hs later have or not a reminder, or a fake working memory task; 48hs after, all 3 groups perform an extinction follow by a reinstatement and different valanced and cognitive systems tasks. We revealed that that the memory reconsolidation interference is effective for the implicit memory.

Cognition, Behavior, and Memory

P160.-Successive retrievals drives a "sad" autobiographical memory resistant to the interfering effect of a positive inductor, possibly mediated by a reconsolidation process

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A previously consolidated memory can enter into a labile state after reactivation, followed by a re-stabilization process defined as reconsolidation. Autobiographical negative memories following reactivation can be modified by the presentation of a positive audiovisual interference, only in women. The aim of this study was to explore if a positive emotional inductor can interfere memory reconsolidation following repeated reactivation sessions of a negative autobiographical memory. On day 1, participant memories were reactivated and after 10 min a positive audiovisual inductor (1R+P) was presented. The second group was reactivated 3 times (3R+ P) separated by 2 days and after the last reactivation session the positive inductor was presented. Memories were tested on experimental day 8. The results showed that the positive emotional inductor did not affect the reconsolidation process after multiple retrieval of a negative autobiographical memory. In sum, these results suggest that repeated retrievals may limit the efficacy of positive audiovisual induction as a potential psychotherapeutic techniques for the modification of dysfunctional autobiographical memories and new studies are necessary to understand how memories becomes resistant.

Cognition, Behavior, and Memory

P161.-The worst and the best memories: Interaction between oposit valence' autobiographical memories

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After reactivation, a previously consolidated memory can enter into a labile state followed by a re-stabilization process defined as reconsolidation. Autobiographical negative memories can be modified following reactivation by the presentation of a positive audiovisual interference, only in women The aim of the present study was to explore if the retrieval of a positive autobiographical memory (the best memory) can interfere the reconsolidation process of a negative autobiographical memory (the worst memory) retrieved before. On day 1, participants' "worst memories" were retrieved and 5 min later they retrieved the best memory (WM+BM group). The control group (WM) retrieved only the best memory. Seven days later all subjects were tested. The presentation of a second event (the best memory) interferes with the emotional expression of the worst memories, only in women.In sum, we found that a positive emotional experience induced by the retrieval of the best memory, after a negative autobiographical memory reactivation, may lead to a change in the emotional information of the original trace and that such effect can be mediated by the reconsolidation process. These

results suggest that a positive emotional induction may be potential psychotherapeutic techniques for the modification of dysfunctional autobiographical memories.

Cognition, Behavior, and Memory

P162.-Behavioral alterations in an NMDA receptor knockout mouse model of schizophrenia mainly emerge after adolescence

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Schizophrenia (SZ) is a chronic mental disorder usually emerging during adolescence and early adulthood that encompasses disruptions in various symptomatic domains, sometimes leading to profound disability. Although its etiology is not yet thoroughly understood, cortical parvalbumin expressing interneurons (PVs) have been pathophysiologically implicated. Also, it is known that PVs normally complete their maturation around SZ onset. We have shown that early postnatal ablation of NMDA receptors in cortical PVs results in an adult SZ-like behavioral phenotype, although its developmental trajectory had not been fully described. Therefore, we aimed to characterize the time course of behavioral alterations, with a special emphasis in presymptomatic stages. To address this, we evaluated mice behavior throughout development, from PND 25 to 20 weeks of age, by means of an open field (OF), a spontaneous alternation Y-maze (YM), nesting and marble burying (MB). Here we confirmed previous findings for OF, YM and nesting, with hyperlocomotion and memory deficit emerging at adulthood. We also found this altered behavior in MB. Remarkably, we found a transient deficit in YM occurring before adolescence. Also, differences were seen between males and females for the first time. In conclusion, while the majority of SZ-related phenotypes induced by early postnatal NMDA receptor ablation emerge in adulthood, some traits may be present at early stages as preclinical entities.

Cognition, Behavior, and Memory

P163.-Modulation of theta band power in dorsomedial striatum signals reward in a virtual reality exploration task

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Oscillations of local field potential activity (LFP) reflect the coordinated activity of groups of neurons and have been associated with network-level computations. Striatal oscillations are modulated during learning and space navigation tasks, and it has been proposed that they can influence information processing between brain structures. However, little is known about the role of striatal LFP oscillations in reward signaling. Using a virtual reality task, we evaluated if theta band LFP modulation in dorsomedial striatum is involved in reward signaling. Head fixed mice explore a virtual linear track. A sequence of licks is required to obtain a reward upon reaching a rewarded area. We used an array of four chronically implanted tetrodes to record single unit and LFP activity in dorsomedial striatum. We found a strong modulation of theta oscillations during our task associated with reward consumption. Interestingly, this increased theta power is absent if the reward is omitted. Also, theta power signaling reward was higher than theta power during running periods. In addition, we found that a big percentage of neurons recorded in dorsomedial striatum are phase-locked to the theta rhythm. To

analyze whether the theta rhythm was locally generated, we performed our analysis with a local reference and found that these theta modulations are still present, which suggests that they are locally generated and a reflection of circuit-level codification of reward in this structure.

Cognition, Behavior, and Memory

164.-Analysis of heart rate trajectories in the study of the emotional processing of children

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Emotions are defined as complex phenomena of short duration, determined by changes in different levels of organization (i.e., physiological, cognitive and behavioral) that occur before significant stimuli or during cognitive processes. Heart rate (HR) is a robust measure of the emotional reactivity involved in the evaluation of these processes. There are few studies that compare performance profiles at different levels of organization to emotional tasks in children. Analyze the trajectories of the HR during Stroop-type task with and without emotional valence in children. A sample of 40 children from 4-8 years old was selected, evaluated with traditional version of the Stroop-type task or an adapted positive emotional version, and the HR was recorded throughout it. The variable of interest was the average of the HR in each trial of the task. A higher HR was found in the children evaluated with the positive emotional condition, compared to the children evaluated with the traditional version of the task. In both groups, the HR presented a gradual increase throughout the trials. The present study incorporates an autonomous variable related to the cognitive performance of the children. The valence task is associated with different patterns ofHR trajectory, which suggests the importance of including this level of organization to analyze the development of emotional processing in children of different ages.

Cognition, Behavior, and Memory

P165.-Effects of acute and chronic physical activity on spatial pattern separation in humans

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The computational process for differentiating similar input patterns has been referred to as pattern separation. It has been reported that BDNF expression in the dentate gyrus is required for memory consolidation of similar, but not dissimilar, spatial representations. Also, several studies showed that exercise can regulate adult hippocampal neurogenesis, which is known to benefit Spatial Pattern Separation in rodents. For these reasons, in this work, we developed a task in an immersive Virtual Reality environment to assess spatial pattern separation and the effect of exercise on this phenomenon. The task consisted on testing the long-term memory with a variable pattern separation load. This was achieved using a similar and dissimilar conditions, where the position of two flags were separated by 20° and 40°, respectively. First, we evaluated the effect of acute physical

activity (Acute) on the consolidation of similar and dissimilar conditions and test them 24 hours later. Also, we studied the phenomenon in a population of athletes (Chronic). Our results showed a significant improvement in memory in the Acute group only in the similar condition compared to the Control group (video of someone exercising). In addition, we observed a trend towards a better performance in the Chronic group, but the difference was not significant. The translational implication of this paradigm could certainly impact on the knowledge of the biological bases of human cognition and mental health.

Cognition, Behavior, and Memory

166.-Newborn and mature neurons contribution to memory engrams

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A fundamental goal of neuroscience is to understand how memories are encoded and stored in the brain. Groups of neurons are thought to serve as the physical representation of memory, the memory trace or "engram". The hippocampus is a brain region highly implicated in memory formation and one of the few regions of the brain with adult neurogenesis in the dentate gyrus (DG). The contribution of immature cells to information encoding and storage is under current investigation. Here we labeled newborn and activated neurons using cfostTA; Ascl1CreERT2; CAGFloxStopTom mice to evaluate their participation in engram formation. During on-Dox diet, these mice were administered with tamoxifen (to express Tomato in newborn neurons) and injected with AAV9-TRE-GFP in the DG. After 4 weeks, mice were moved to off-Dox diet for 2 days to express GFP in activated cells when exposed to an enriched environment (EE). Our preliminary results showed that the proportion of activated newborn neurons after EE was higher than the mature neurons activation suggesting that young granule cells would be more likely to be recruited into engrams. To further evaluate the contribution of newborn neurons to other hippocampal dependent behaviors, we are conducting experiments training the transgenic mice in a head-fixed apparatus to perform a GO/NO GO discrimination task in a virtual reality environment. These experiments will shed light on the contribution of newborn neurons to contextual memory engrams.

Cognition, Behavior, and Memory

P167.-Social decision-making in chronic ecstasy users

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Previous works have shown that acute 3, 4-methylenedioxymethamphetamine (MDMA) administration and chronic consumption of ecstasy (i.e. MDMA street name) alters social cognition on a variety of domains, including social decision-making. However, this research has suffered from several methodological limitations (mainly, extensive polysubstance use among ecstasy users). Furthermore, there is no evidence to date relating chronic ecstasy use and complex social decision-making processes such as bargaining. In this study, we intended to address this gap in addition to overcoming limitations of previous works. We compared 22 ecstasy users (EXT)

with exceptionally low polysubstance (defined as less than 10 occasions of use of other substances) use with 11 cannabis-only users (CAN) and 12 alcohol-only users (ALC) on an iterative version of the Ultimatum Game (UG) in which subjects played as the proposers against simulated respondents. All groups showed preserved basic bargaining indexes. Nevertheless, there was a marginally significant difference (p = .059) between groups in the mean value of hyper-fair offers (>50% of the money offered to the other player). The EXT group offered significantly more than the ALC group but not than the CAN group. There were no differences between the ALC and the CAN group in this measure. Our results suggest that ecstasy users do not display decision-making deficits and under certain circumstances, they behave more altruistically.

Cognition, Behavior, and Memory

P168.-Mice hippocampal synaptic composition and non-histone protein acetylation

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Protein acetylation is a post translational modification involved in gene transcription, DNA damage repair, cell division, protein folding and metabolism. The enzymes responsible for the transfer and removal of acetyl groups are lysine acetyltransferases (KAT) and lysine deacetylases (KDAC) respectively. KDACs are classified by its subcellular localization, principally nuclear or cytoplasmic. Protein acetylation affects synaptic plasticity and memory, but its effects on synaptic composition are poorly understood. There is evidence that protein acetylation at synapse promotes the dendritic clustering of PSD95 in cultures of hippocampal neurons. In this study we found an increment of PSD95 clustering in mice hippocampal extracts after 45 minutes of inhibitory avoidance task respect to control animals. Moreover, an augmented level of non-histone protein lysine acetylation was found and it positively correlates with that of PSD95 in post synaptic densities, indicating a possibly causal relation. Similar results were found in primary culture of hippocampal neurons after chemical LTP. Finally, post training administration of Tubastatin A (an HDAC6 inhibitor) facilitates long-term memory consolidation after inhibitory avoidance task. These results strongly suggest that protein acetylation has an important role regulating the synaptic changes that occur during memory consolidation.

Cognition, Behavior, and Memory

P169.-Active avoidance learning increase proliferation of neuronal progenitors in the Dorso-medial pallium of adult zebrafish

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One of the principal forms of adult neuronal plasticity is the integration of new neurons into preexisting brain circuits. The study of network remodeling by adult neurogenesis involves complex relationships between newly-added neurons, preexisting networks, and neuronal activity. Zebrafish is an excellent organism to study the activity-dependence of network remodeling, since it exhibits numerous cognitive abilities and adult neurogenesis occurs throughout their brain. In this work we trained adult zebrafish to achieve an Active

Avoidance task. Trained individuals show a daily improvement in their avoidance responses during 4 consecutive sessions. Moreover, the trained zebrafish exhibits a long term memory of the task, evaluated 24 hours after the last training session. To address the role of cognitive activity in network remodeling we evaluated neuronal progenitor proliferation in the zebrafish pallium. We found that active avoidance training induces a two-fold increase in the proliferation of neuronal progenitors in a discrete sub-region of the Dorso-medial pallium. This finding leads us to plan further experiments to interrogate the role of this cognitive activity on other aspects of adult neurogenesis, as neuronal fate, synaptic integration, and neuronal survival.

Cognition, Behavior, and Memory

P170.-Extinction learning efficiency in *Neohelice granulata* depends on the proximity to the original memory acquisition. An explanation correlated to the NMDA receptor surface expression dynamics

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Context-signal memory (CSM) in the crab *Neohelice granulata* depends on NMDA receptor activity. The surface expression of the GluN1 subunit of the receptor is altered during consolidation in the central brain: while the total amount of the receptor remains constant, surface expression of GluN1 is down-regulated immediately after training, up-regulated 3 hr after training and returns to naive and control levels 24 hr after training. A possible interpretation is that the decrement immediately after training wouldn't allow further activation through the receptor, affecting the incorporation of new information to the previous memory. On the contrary, the increment 3-hr post-training, once the consolidation process is advanced, could reflect a higher probability of activation, facilitating the addition of new information. To test this, we focused on the extinction learning (also dependent on NMDA receptor activity), enabling a second learning event at the post-training time points when surface expression is altered. Our results show that the extinction protocol has different outcomes when applied at different times: immediately after training, no extinction is found in the retention of CSM; on the other hand, when applied 3 hr post-training, a significant decrease in the retention of CSM occurs, indicating extinction. The results suggest that the maturation of memories shows different capabilities to add information and that these variations correlate to NMDA surface expression.

Cognition, Behavior, and Memory

P171.-Role of 5-HT2A receptor in social cognition in mice

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The serotonergic system and more precisely the serotonin type 2A receptor (5-HT2AR) is involved in a wide variety of cognitive and emotional functions. In recent studies, it has been found that 5-HT2AR participates in the prosocial effects of certain drugs. Moreover, the social cognitive impairments observed in different psychiatric disorders, such as schizophrenia and Asperger syndrome, have been associated with a hypofunction of the 5-HT2AR. However, the mechanisms underlying this phenotype remain unclear. In the present study we analyzed the role of 5-HT2AR in social preference (SP) using a genetically modified mouse model that presents a

constitutive depletion of the5-HT2AR (KO) compared with their wild type mates (WT). For this purpose we performed a three-chamber sociability test. We also explore how SP can be affected by an increased level of serotonin in the central nervous system via chronic administration of fluoxetine. We observed that both male and female KO mice had a lower social preference compared to WT. Thus, the chronic administration of fluoxetine increased social preference only in WT mice. These results suggest that the serotonergic system could be involved in SP and that its participation could mediated at least partially by 5-HT2AR.

Cognition, Behavior, and Memory

172.-Norms for emotional words in Spanish: Preliminary findings from an Argentinian adaptation of the Affective Norms for English Words

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The Affective Norms for English Words (Bradley & Lang, 1999) are a normative set of verbal material rated by a sample from the United States on valence, arousal, and dominance. The aim of this study was to adapt this set and provide a normative pool of emotional words for Argentina. The 1034 words from ANEW were translated and adapted to Rioplatense Spanish by three bilingual judges, until reaching complete agreement. Then, all 1034 translated words were randomly divided into 6 lists. Two-hundred volunteers (166 women, range: 18 – 52 years) from the Buenos Aires Metropolitan Region received one word-list and they were instructed to assess each item according to its valence, arousal and dominance, through the Self-Assessment Manikin. The results indicated that valence and arousal conformed to a quadratic distribution similar to the one found on the original sample. Regression analysis showed a significant relationship between valence and arousal, which explained 26.5% of the variance. Furthermore, there were no differences in the valence ratings between the US and the Argentinian sample; however, the latter showed higher ratings for arousal and dominance. While normative scores for emotional stimuli are widely used in neuroscientific research, culturally-specific instruments are not always available. The results from this study represent a first step towards reliable and valid instruments to assess the verbal aspects of emotion in Argentinian populations.

Cognition, Behavior, and Memory

P173.-Dopaminergic and Noradrenergic systems control protein synthesis during the behavioral tagging process underlying memory reconsolidation.

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Our recent findings show that memory reconsolidation relays on a behavioral tagging process. That is to say, the event which triggers memory reconsolidation induces both the setting of a tag, which later decides where memory will be stored, and the synthesis of plasticity related proteins (PRPs) that will be captured at the tagged sites for memory reconsolidation to occur. Our current work focuses on identifying the neurotransmitter systems and the brain structures that regulate the synthesis of PRPs. Using the spatial object recognition (SOR) task, we show that the infusion of the D1/D5-dopaminergic receptor antagonist SCH23390, or the β-adrenergic

receptor antagonist propranolol, 15 min before the reactivation of SOR memory induced long-term retrograde amnesia. Interestingly, the exploration of a novel open-field within a restricted time window overcame the amnesic effect of both antagonists, rescuing memory reconsolidation. In addition, the electrical stimulation of the ventral tegmental area (VTA) or the locus coeruleus (LC), 60 min before the reactivation session, also prevented the amnesic effect of emetine infusion in either CA1 or dentate gyrus, respectively. In summary, our results suggest that the VTA and the LC act over the hippocampus via the D1/D5-dpaminergic and the β-adrenergic receptors, thus regulating the synthesis of those proteins required during memory reconsolidation.

Cognition, Behavior, and Memory

P174.-Effect of brain masculinization in a mouse model of autism

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Autism spectrum disorders (ASD) are characterized by reduced sociability, diminished communicative skills and repetitive behaviors. Notably, the proportion between boys and girls diagnosed with ASD is about 4:1. To identify the biological mechanisms involved in this bias, we use a mouse model of ASD: the prenatal exposure to valproic acid (VPA). Recently, we observed that this model also presents a different phenotype in males and females, as females do not show the reduction in sociability observed in adult males. Our hypothesis is that the masculinization process that male brains experience during development is necessary for VPA prenatal exposure to affect autism-related behaviors, neuronal alterations and gliosis. To test this hypothesis, we study the effect of brain masculinization of female mice on the VPA model. In rodents, normal masculinization of some brain regions involves inflammatory signaling molecules. At the same time, a striking risk factor for ASD corresponds to deregulations of the immune system. So, the natural process of masculinization increases inflammation in males and pushes males closer to a threshold of vulnerability that can be more easily reached if inflammation occurs during a sensitive developmental period. We hypothesize that VPA female mice will show impaired sociability after a masculinization protocol. Our preliminary experiments demonstrate indeed that masculinized VPA females show alterations in sociability.

Cognition, Behavior, and Memory

P175.-Modulation of ultrasonic vocalizations by chemical stimuli to assess olfactory function in mouse pups

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The rate of ultrasonic vocalizations emitted by mouse pups can be modulated by a variety of conditions, including age, maternal separation and exposure to olfactory stimuli, and the degree of modulation varies depending on mouse strain. Here we addressed whether neonatal ultrasonic vocalizations were susceptible to maternal potentiation and to inhibition by the presentation of aversive olfactory stimuli in a transgenic mouse line that fluorescently reports glial cells (S100B-GFP mice), previously uncharacterized for these responses. We found that the rate of ultrasonic vocalizations during the first 5 minutes after nest separation peaked at the end of the first postnatal week. Nest separation of 1-week-old mouse pups during 5 minutes followed by re-exposure to the nest (mother plus littermates) for another 5 minutes produced potentiation of the rate of

ultrasonic vocalizations, emitted in the 75-85 kHz frequency band, by 90 ± 31 %, from a basal value of 12 ± 8 vocalizations per minute. In addition, the aversive odorant citral diluted at 10 % produced an inhibition of 76 ± 10 % of the rate of vocalizations after maternal potentiation, while citral diluted at 1 % had no inhibitory effect. These data are consistent with published work characterizing other mouse strains and sets the starting point to explore the sensitivity of ultrasonic vocalization inhibition by aversive olfactory stimuli to evaluate differences in olfactory thresholds.

Cognition, Behavior, and Memory

P176.-Neural mechanism involved in contextual memory: role of CA3 and CA1 remapping

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The Hippocampus (HP) is involved in encoding, consolidation and retrieval of episodic memories. Some hippocampal neurons, place cells (PC) are tuned to spatial location and generally change their tunning when an animal change context (remapping). It has been suggested that the hippocampal ability of storing and distinguishing between different situations and contexts can be related with place cell's remapping.
Several studies have shown how PC can either remap or not as a consequence of changes in the environment. It is also known that there are differences between CA1 and CA3 (two hippocampal regions) in spatial codification. Still, there is no study showing the link between the memory that the animal is expressing and the activity of its neurons. In other words, It's still unknown whether when an animal recognizes a certain context as new, there is remapping in the HP or not. The aim of this project is to understand how the differential remapping observed in CA1 and CA3 correlates with the behavioral response. To answer this question we use a behavioral task thatallowed us to discriminate if an animal recognizes a context as new, or as one they already knows. We carried out electrophysiological recordings in CA3 and CA1 region of the HP while they were performing the tasks in order to correlate the remapping and the evocation of different contexts.

Cognition, Behavior, and Memory

P177.-Long-term memory impairment is different in male and female transgenic McGill-R-Thy1-APP rat model of Alzheimer´s disease

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Memory impairment in early Alzheimer Disease (AD) would rely on an increase in soluble Aβ-oligomers, potent neurotoxins altering synaptic plasticity. McGill-R-Thy1-APP Wistar-transgenic (Tg) rats bearing human Amyloid Precursor Protein gene with Swedish and Indiana mutations of familial AD offer an opportunity for testing sex differences in cognitive deficits at AD onset. Homozygous Tg rat already showed cognition deficits at 3 month and intraneuronally human Aβ accumulation from 1st week. Hemizygous Tg (He) show a more subtle phenotype and do not develop extracellular plaques even at 20 months. 12-13 month old (mo) He male (m) and female (f)

rats and their wild type litter-mates (WT) were left to explore an open field (OF) for 5min and tested 24hr later; bi-dimen-sional exploration was quantified, being significantly lower in test than in training, denoting habituation. Same rats were trained in a 2-object recognition (OR). WT and Hef, and WTm, discriminated new vs known object 1hr (short-term memory, STM), and 24h (long-term memory, LTM) later, while Hem rats did not. Rats were trained in an inhibitory avoidance step-through (IA), where latencies to avoid a mild footshock were recorded. 24h later/ Test latencies were significantly higher for WT and Hef. and WTm, while there was not significant difference for Hem rats. Hence, 12-13 mo He Tg male rats, though not females, suffer selective STM/LTM deficits, in associative memories with spatial and/or aversive components.

Cognition, Behavior, and Memory

P178.-When does the mammalian GPS use the dentate gyrus in everyday challenges of spatial navigation?
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Our mammalian GPS, Global Positioning System, is made of diverse brain structures such as the dentate gyrus (DG) of the hippocampus. This is one of the most plastic brain regions because it has adult neurogenesis and this process is modulated by the animal experiences.The most accepted function of the DG and its new neurons is the discrimination of similar spatial contexts. However, their contribution in an ordinary behaviour remains unknown. We started investigating the hypothesis that the DG would be necessary to solve difficult spatial challenges but not easy ones in a goal guided behaviour. Therefore, adult mice were infected with AAV flex-hM4Di plus CAG-Cre retrovirus in the DG to allow chemogenetic manipulation of neuronal activity in mice navigating in a crossword maze after the i. p. injection of the synthetic agonist clozapine-N-oxide ("CNO") or its vehicle ("control"). In a single day mice had to learn two shortest paths to a new reward location. We designed spatial routes of two levels of cognitive demand and evaluated mice performance with or without chemogenetic inhibition (CNO vs. control). Easy and difficult journeys were equally solved and learnt by mice under control condition. However, mice receiving CNO could only learn easy spatial trajectories but not the difficult ones ($p = 0.01$, Wilcoxon signed rank test, $N = 4$ mice). Therefore, our preliminary data suggest that the DG is required by the GPS during spatial navigation in complex mnemonic challenges.

Cognition, Behavior, and Memory

P179.-Different responses in anxiogenic-like behavior and motor coordination in CB1+/- and CB1-/- mice
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Given that the CB1 receptor (CB1) has been associated to mood and behavior, the aim of this study was to evaluate the effects of CB1 deficiency in behavioral paradigms of anxiety and depression.
Male CB1 knockout mice (CB1-/-), heterozygous CB1+/- and CB1+/+ were tested in behavioral paradigms. Open field (OF), elevated plus maze (EPM), light-dark box (LDB) and rotarod tests were carried out to evaluate anxiety-like behavior and motor coordination. Novelty-suppressed feeding (NSF), sucrose splash and forced swimming

test (FST) were performed to evaluate depression-like behavior. In EPM and LDB, the number of entries and time spent in the aversive area was lower in CB1-/- but not in CB1+/-. In OF, EPM and LDB, explorative parameters were decreased only in CB1-/-. In the rotarod test, CB1-/- did not improve motor performance after training while CB1+/- improved it after repetitive training. NSF showed no differences in intake latency but a reduction in CB1-/- food intake. The sucrose splash test revealed a reduction in latency to groom and time of grooming in CB1-/-, and the FST showed longer immobilization during the last period of time. In conclusion, CB1-/- exhibited deficits in motor coordination, anxious and depressive behavior. However, CB1+/- showed alterations in motor coordination but not in anxiety-like behavior. These results could explain the role of CB1 in behavioral parameters, which may correlate with CB1 polymorphism observed in depressive patients.

Cognition, Behavior, and Memory

P180.-Lack of CB1 receptor on GABAergic neurons: effects in a pharmacological model of schizophrenia

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Schizophrenia is a chronic and progressive mental disorder that combines a variety of clinical symptoms, including psychosis, anhedonia and cognitive deficits. Although the precise mechanisms responsible of schizophrenia development are unknown, several models demonstrate the involvement of dopaminergic, glutamatergic and gabaergic neurotransmission systems. In addition, a cannabinergic hypothesis has been put forward. Endocannabinoid levels and cannabinoid receptor type one (CB1) signalling hence have been implicated in schizophrenia owing to their neuromodulatory role. The aim of this study was to evaluate the contribution of CB1 receptor on GABAergic neurons in psychosis like states using the model of acute systemic administration of the N-Methyl-D-aspartate type ionotropic receptor (NMDAR) antagonist, MK-801 in wild type (WT) and GABA-CB1-KO mice. Locomotor activity was measured in open field at 30, 60 and 90 minutes after injection. Locomotor activity in vehicle-treated GABA-CB1-KO did not differ significantly from vehicle-treated WT mice, however MK-801 induced hyperlocomotion persisted longer time in GABA-CB1-KO than WT littermates.
This results indicate that CB1 receptors activity on GABAergic neurons protect from the susceptibility to generate a persistent psychotic-like response. This result is however in contrast with the attenuation of psychotic responses observed by pharmacological CB1 antagonism or complete deletion of CB1 deletion.

Cognition, Behavior, and Memory

P181.-Influence of target trajectory on auditory peripersonal space threshold estimations for sound sources approaching or receding in discrete steps

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To effectively navigate and interact with their environment, humans need to integrate information on the position of the body and on the space around the body (peripersonal space, PPS). The PPS is often described as having a single, distance-based, dichotomic boundary within which stimuli elicit enhanced neural and behavioral responses. However, recent studies have shown that PPS-related measures are not binary and that boundaries can shrink or expand as a function of the properties of the stimulus, including factors not related to the actual stimulus position. One of such factors is the stimulus trajectory. It has been reported that the PPS expands or shrinks depending on whether the auditory stimulus is approaching the body or receding from it, respectively. As far as we know, all of the previous studies that reported such modulations used sources with continuous movement. In this study, we aim to determine if this effect can be elicited by sound sources moving in discrete steps, a kind of trajectory that we consider more ecologically valid. By measuring the reachability to a sound source, we found an overestimation of the auditory PPS threshold when sources approached the listeners. In contrast, when the sources were receding or describing random trajectories, the PPS threshold was in close accordance with the participant's static reach.

Cognition, Behavior, and Memory

P182.-A behavioral-tagging perspective of spaced learning: ERKs1/2 kinases play a dual role in LTM formation during a spatial object-recognition task

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The superiority of spaced over massed learning is an established fact in the formation of long-term memories (LTM). Here we addressed the cellular processes and the temporal demands of this phenomenon using a weak spatial object recognition (wSOR) training task, which leads to a short-term memory (30 minutes post training) but not to LTM (24 hours post training) of spatial object location. We observed SOR-LTM promotion when two identical wSOR training sessions were spaced by an inter-trial interval ranging from 15 minutes to 7 hours, consistently with spaced training. The promoting effect depended on neural activity and protein synthesis in the dorsal hippocampus. Based on the "behavioral tagging" hypothesis, which postulates that learning induces a neural tag that requires proteins to form LTM, we propose that retraining mainly retags the sites initially labeled by the prior training. Thus, when weak, consecutive training sessions are experienced within an appropriate spacing, the intracellular mechanisms triggered by each session would add, thereby reaching the threshold for protein synthesis required for memory consolidation. In addition, our results suggest that ERKs1/2 kinases play a dual role in SOR-LTM formation after spaced learning, both inducing protein synthesis and setting the SOR learning-tag.

Cognition, Behavior, and Memory

P183.-Declarative memory enhancement in older and young adults

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The stored information can re-enter a labile state after the presentation of a memory cue (reminder) followed by a period of re-stabilization known as reconsolidation. During this process the memory trace can be modify, impaired, strengthened or changed in content. Whether the process of reconsolidation is conserved in elderly is still under debate. Normal aging is associated with deficits in memory processes and it has been suggested that reconsolidation is also affected by aging. Here, we studied whether a declarative memory could be strengthened in older adults through the reconsolidation process. We performed a three day experiment with six groups (in young and older adults). On day 1, participants learned sound-word associations, on day 2 they received no reminder (NR group), one (R group) or two rounds of reminder presentation (Rx2 group). They were tested on day 9. The main results showed that unlike young adults, the R group did not increase memory persistence in older adults; on the contrary it had the same performance as the NR group. However, the Rx2 group recalled better the learned associations than the other two groups on day 9, suggesting that repetitive reactivations trigger memory strengthening in older adults. Thus reconsolidation could be used as a tool to improve episodic memories that are critically impaired in elderly.

Cognition, Behavior, and Memory

P184.-Auditory distance perception in peripersonal space: Effect of tactileexploration on reaching measures

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We conducted an experiment in which the participants had to estimate if a sound source was reachable (auditory peripersonal space, APS) and to estimate its distance (auditory distance perception, ADP) by reaching to a small loudspeaker. Participants were assigned to Experimental (EG) and Control (CG) groups. They resolved three conditions in the following order: Pretest–Test–Posttest. In Test condition, the CG repeated the same task performed in Pretest and Posttest without any feedback, whereas the EG resolved a tactile exploration phase in which they were able to touch the sound source. We studied the effects of tactile exploration feedback on both reaching measures. We characterize the participants' responses and provide evidence that tactile exploration feedback significantly reduces the response bias of both the perceived boundary of the APS and the ADP of sound sources located within reach. In case of CG, the repetition of the task does not affect APS and ADP accuracy, but improves the performance consistency.

Cognition, Behavior, and Memory

P185.-Measuring children's executive functions in educational settings with unsupervised software.Mate Marote: a meta-analysis.

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Mate Marote is an open source cognitive-training software aimed at children between 5 and 8 years old. It consists of a set of computerized games specifically tailored to train executive functions (EF): a class of processes critical for purposeful, goal-directed behavior, including working memory, planning, flexibility, and cognitive control. During the last ten years several studies were performed using this software to measure and train children EF at their own schools in supervised interventions. At present, we are starting to conduct unsupervised, but controlled, interventions with children's own teachers help. To make sure that results of supervised and unsupervised evaluations are comparable, we performed a meta-analysis with the results of a baseline test phase to study the differences between the two intervention modalities. The analysis includes the performance of 415 5-to-8-y.o. children from 13 different schools of 4 urban environments. In the present study we show that children EF performance obtained in unsupervised interventions is mostly comparable to the data collected in the testing phase of supervised settings, at least for 3 of the 5 tests included. Further studies are required to understand whether the other 2 tests can be used to measure EFs in unsupervised interventions.

Cognition, Behavior, and Memory

P186.-Exploring the function of the serotonin 5-HT2a receptors in the mechanism underlying retrieval induced forgetting in rats

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Over the past several decades, neurobiological research on memory has been focused on the mechanisms underlying memory storage. Nevertheless, the study of forgetting and, specifically, active forgetting has been increased since Anderson et al. showed in 1994 that the retrieval of certain memories could cause the forgetting of related, but not explicitly evoked information by a mechanism called retrieval-induced forgetting (RIF). The behavioral paradigm used to characterize this phenomenon in humans was then adapted for rats, opening the possibility to perform causal studies. As with humans, in rats, RIF is competition-dependent, cue-independent, and reliant on the prefrontal cortex. This work aims to explore if and how the serotonergic system participates in RIF. Specifically, we used an antagonist of the serotonin receptor 2A in the medial prefrontal cortex and in the dorsal hippocampus in two separate experiments. We hypothesize that only the animals exposed to the conditions that promote the retrieval-induced forgetting will be susceptible to the effect of the drug and will show memory for the competing item. RIF could be thought of as a mechanism for optimizing the storage and use of information that can guide behavior, thus, its neural mechanisms are relevant for the understanding of adaptive memory in rodents and humans.

Computational Neuroscience

P187.-Encoding and decoding properties of different dentate gyrus age populations

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The intrinsic properties of neurons in a population are diverse and distinct spiking outputs may arise from this heterogeneity, reducing redundancy in the population. Due to the continuous birth of granule cells in the dentate gyrus, neurons of different ages receive, process and convey information at any given point in time. While maturing, granule cells develop their intrinsic properties in a stereotyped way producing a structured heterogeneity in the population. We hypothesize that young neurons play an active role in the processing of information already in their immature state. We study how neurons of different age transform their input by performing whole cell recordings and injecting fluctuating currents simulating in vivo observations. By fitting Generalized Linear Models to our data, we can predict spiking with a high degree of accuracy while getting a reduced characterization of the recorded neurons.We use these characterizations to compare the encoding properties between the different age populations. Do different populations represent stimuli in the same way? We explore this question by using the encoding models of the different neurons to carry out model-based decoding. We can decode stimuli using different age neurons to explore what features of the stimuli are preserved in the spiking response and compute information measures. Using groups of neurons from the same and different populations we can analyze synergy and redundancy in the populations.

Computational Neuroscience

P188.-Prediction of patient's response to psylocybin treatment for depression using Gradient Boosting Machine Learning based on Baseline fMRI Data

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Classic psychedelics act by agonism to the 5HT2A receptor and have the capability to produce profound and transient alterations in consciousness. Recently, important advances in their therapeutic properties have been reported and treatmentsfor variouspsychiatric conditions are currently being assessed. In particular, in this work we study the effectiveness, measured by the reduction of severity indices, of therapies with Psilocybin in patients with treatment-resistant major depression. To perform the prediction of patient remission, a sample of functional magnetic resonance imaging (fMRI) data from 16 patients was used. The classification with gradient boosting was carried out based on the hypothesis that the baseline state contained relevant information to predict what was reported by the patients after the supply of Psilocybin. The neural correlates of the treatment response which emerge from our analysis agree with the previously reported brain areas associated with this condition, comprised mainly by the limbic system. Our results suggest that treatment response can be differentiated using baseline neuroimaging, in particular fMRI, and begin to trace a path towards individual-oriented treatments for this condition.

Computational Neuroscience

P189.-Modular structure of multilayer temporal functional connectivity networks during loss of consciousness

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Consciousness can be defined as reflecting subjective experience, or as the sense of being a distinct entity capable of agency, sentience, narrative identity in time. In the transition to unconscious states, these subjective attributes are lost. The study of the neural correlates of this change could shed a light towards understanding consciousness itself. The dynamic core hypothesis proposes that neural correlates of consciousness are to be found in a constantly evolving functional cluster of thalamocortical regions. We investigated the modular structure of multilayer functional connectivity networks measured with fMRI during conscious wakefulness, deep sleep and propofol induced states. We introduced a null model based on two dynamic processes unfolding on networks with power law distributions for degree and community sizes. After using this model to select the resolution and inter-layer coupling parameters, we applied a community detection algorithm on the multilayer network of temporally evolving functional interactions inferred from fMRI. Both propofol induced unconsciousness and deep sleep decreased the size of the largest dynamic community, which could be attributed to sensory regions coalescing into larger communities, while frontoparietal regions showed the opposite effect. Our results comprise a method for parameter selection in multilayer modularity maximization algorithms and for the characterization of time-evolving functional modules during loss of consciousness.

Computational Neuroscience

P190.-Plug and Play spike sorting based on wavelet analysis and a genetic algorithm

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Spike Sorting is the procedure of grouping together action potentials belonging to the same cell, while separating these from action potentials belonging to other cells. As seen from a given extracellular electrode, spikes from different neurons present different shapes, and spikes from one particular neuron roughly retain shape even during very long-term recordings; thus, spike-sorting algorithms rely, in part, on spike shape for classification. Due to the amounts of data collected, spike-sorting by hand becomes impossible for more than a few seconds, and a few electrodes. Even semi-automatic spike-sorting methods, where the final user decides whether a group of spikes does or does not belong to the same neuron are not recommended as they require a human taking decision which might be biased or operator-dependent. Moreover, spike sorting is part of a chain of tools used to analyze experimental data, or decide the site for clinical deep-brain stimulation electrode implants in Parkinson's disease. Given the importance of the procedure, a fully automatic, real-time spike sorting algorithm is desired, and some have been proposed. Here we present a spike sorting algorithm that can run in near-real time, based on wavelet encoding of spikes and a genetic algorithm for sorting. The number of clusters is automatically determined (a parameter usually hard to optimize). The performance of this algorithm is compared to a popular spike-sorting algorithm, with good results.

Computational Neuroscience

P191.-Diversity on brain dynamics: modernity may influence brain alpha oscilations and complexity

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Brain diversity studies are focused mostly in developed countries. Recent studies found that a sub-group of people from geographically-isolated regions in India lacks the alpha rhythm and their EEG signal complexity is lower. The objective of this study was to identify the degree of divergence in brain dynamics for an Argentine population. Four hundred and thirty-seven participants from different provinces signed an informed consent and completed a demographic survey. EEG samples with open and closed eyes were taken from the participants using the Emotiv EPOC+ (14 electrodes) device. Signals were analyzed, obtaining the energy in the alpha band, its peak frequency and a signal's complexity coefficient (Lempel-Ziv), and with that data urban and non urban populations were compared. Open eyes measurements from participants from isolated regions showed lower peak frequency on every channel, except for P8, as well as less energy in the alpha band on seven channels and lower complexity on every channel. Closed eyes measurements from participants from isolated regions showed lower peak frequency, alpha band energy and complexity for every channel. These findings suggest that modernization may have an influence in brain dynamics and that an "average" brain may not exist. Findings allow to conclude that social and environment factors influence brain dynamics, stressing the importance of having comparative worldwide data.

Computational Neuroscience

P192.-Unveiling the stimulus features modulating the correlations between neurons: Application to mouse ganglion cells

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A crucial question in computational neuroscience is whether the correlations between neurons encode sensory information, and whether this information is different from the one encoded by individual cells. In this work we propose a straight-forward method for extracting the stimulus features triggering positively or negatively correlated neuronal activity. The basic hypothesis is that correlations are modulated by a low-dimensional subspace of the stimulus that need not coincide with the one derived under the independence hypothesis from the receptive fields that modulate the firing of each individual cell. Given that the naïve estimation of this relevant subspace is mathematically ill-defined, we here derive a Bayesian estimator that is robust in the limit of few data samples. When applying the method to ganglion cells in the mouse retina that are stimulated with white-noise visual input, we find that the receptive fields governing correlations tend to be spatially localized, and that they differ from those governing individual neurons. The approach here presented is applicable to arbitrary sensory modalities, and reveals those stimulus features that are responsible for the synergy in the neural code, which so far have remained hidden, or perhaps marginalized into single-cell receptive fields.

Computational Neuroscience

P193.-Non-linear dimensionality reduction techniques for spike sorting

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Spike sorting is a key step in the processing of extracellular electophysiological data, in which recorded spikes are clustered based on their shape, ideally reflectingthe different neurons that originated them. The improvement in the acquisition hardware has allowed an exponential growth in the number of neurons that can be registered in parallel, but spike sorting algorithms have not advanced at a similar pace. In this work, we present a comparative study between two dimensionality reduction algorithms that could improve manual and automatic sorting: t-SNE and UMAP. We performed an exhaustive search based on a small dataset of recordings to find the best hyperparameters for each algorithm by evaluating the quality of the generated projections with five clustering-goodness measures and two ad-hoc measures based on superposition and classification accuracy. We found that metric=Euclidean and learning rate=1 for UMAP and metric=Braycurtis or Chebyshev, perplexity=80 and learning rate=1000 for t-SNE, represent the best compromise in performance. While both algorithms separated clusters much better than traditional methods, UMAP outperformed t-SNE in clustering-goodness metrics and computation time. We next plan to test the limitations of these algorithms in artificially large databases pooling data from different recordings. The results presented in this work offer an encouraging picture for the application of non-linear dimensionality reduction techniques tospike sorting.

Computational Neuroscience

P194.-Trail Making Test revisited: Patterns of visual and manual trajectories as markers of executive processes
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The Trail Making Test (TMT) is a neuropsychological test widely used for decades for the diagnosis of executive dysfunctions in a set of neurological and psychiatric conditions. The TMT has two parts: A) participants have to connect 20 consecutive numbers and B) both numbers and letters are connected in an alternate order (1-A-2-B, etc). It is a complex task, and involves different stages supported by distinct executive functions. Surprisingly, it is done with paper and pencil, and only the total time is quantified. We designed a computer version of the TMT in order to study, with more resolution and precision, the components of the task in healthy participants and patients, providing a deeper understanding of the underlying processes involved in performing a traditional test. We measured both hand and gaze position. We found that total time (part B vs A) is similar to the traditional version. Concerning eye movements, saccades are similar in A and B, but there are fewer fixations in A. Moreover, we found a longer lag between gaze and hand in B, explained by a delay in the outgoing hand movements but not in the gaze. Using both hand and eye movements we are able to parse the whole task into different stages, opening the possibility of exploring them in terms of different executive functions. Finally, a standardized evaluation of executive functions was collected to validate the digital TMT measures.

Computational Neuroscience

P195.-The effects of LSD on the organization and content of natural language assessed by computational semantic and non-semantic analyses
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Serotonergic psychedelics are known to induce profound changes in human perception and cognition. It has been suggested that these effects mirror psychosis and that they reflect increased entropy of neural activity. We investigated a prediction following from these hypotheses, namely that language produced under the effects of lysergic acid diethylamide (LSD) should present reduced semantic coherence. Computational semantic analysis of interviews conducted after 75 µg of intravenous LSD verified this prediction. Non-semantic analysis of speech organization revealed increased verbosity and reduced lexicon, indicating higher recurrence and disrupted temporal ordering compared to language produced under placebo. These changes are more similar to those observed during manic psychoses than in schizophrenic patients, and are in line with heightened neural entropy. Importantly, features related to language organization allowed machine learning classifiers to identify speech under LSD with accuracy comparable to that obtained by examining semantic content. These results constitute a quantitative and objective characterization of disorganized natural speech as a landmark feature of the psychedelic state. Higher brain entropy has been proposed as a putative mechanism for the therapeutic action of psychedelics, suggesting that the analysis of natural language can play an important role in the prediction and monitoring of the therapeutic effects associated with these compounds.

Computational Neuroscience

P196.-Dynamics of GABABR signaling: influence of cholesterol and aging

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GABA B receptors (GABABRs) are obligatory heterodimers which belong to the superfamily of G protein-coupled receptors (GPCRs). Age-related changes in membrane cholesterol levels modulate membrane fluidity, which in-turn influences GPCRs´ localization and function. We studied the GABABR and also a transmembrane transporter structurally homologous to KCC2. To characterize transient conformational changes over time, molecular dynamics simulations were performed using a neuronal plasma membrane (PM) model. Two different membrane cholesterol levels were evaluated: 45% and 10%, which intend to resemble the composition of adult and aged neuronal PMs, respectively. For experimental verification in both young and aged cerebella, we determined protein expression and distribution, and we assessed whether the two proteins interact with each other in vivo. Techniques were: western blots (WB), co-immunoprecipitation assays, and multiple immunolabeling followed by confocal microscopy. Our results suggest that the expression and spatial distribution of both proteins change as the cerebellum grows older. Based on our in silico analyses, we infer that a G protein-independent interaction does occur. Also, we confirmed that the two proteins are part of the same complex in the cerebellum. As our simulations indicate, we propose that the underlying mechanism implies transient conformational changes, which are highly dependent on cholesterol levels and are therefore affected by the aging process.

Computational Neuroscience

P197.-Predicting psychiatric drug subjective response using graph convolutional neural networks

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Precise identification of patient's feelings, state of mind and mood is of paramount importance when diagnosing psychiatric disorders and evaluating the response pharmacological treatments. In general, an accurate prediction of the subjective experience of a person under the influence of psychoactive drugs, which is the result of the drug's complex interactions with a number of neural receptors, implies a technical and methodological challenge. These subjective experiences may be objectively described from unstructured written reports, using natural language processing algorithms. Graph convolutional deep neural networks is a booming and powerful machine learning strategy applying sequential convoluting operations on graph encodings (such as pharmaceutical compounds or natural language reports) extracting relevant features hidden in the input samples. In these networks, each of the convolution layers extracts local patterns or sub-features that have eluded previous strategies. Both molecules and speech structure can be represented as graphs, in which nodes could correspond to atoms or words, and edges correspond to bonds or grammatical relationships, respectively. We were able to extract relevant features of the drug-receptor interactions and predict their response, for instance, in terms of natural language descriptions of patients or users of the compound. The current work represents an effort towards y linking computational chemistry, medicine and language processing.

Motor Systems

P198.-Muscular activity decline in a Parkinson's disease animal model

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Parkinson's disease diagnosis is currently based on characteristic motor dysfunctions induced by the dopaminergic neurons depletion in the substantia nigra pars compacta (SNpc). The most common Parkinson's disease animal model induces massive nigrostriatal degeneration by intracerebral infusion of 6-hydroxydopamine (6-OHDA). Using chronic implanted EMG electrodes in a hindlimb muscle of freely moving rats, we evaluate the effect of the PD neurotoxic model in the muscular activity. Power spectrum density (PSD) from each EMG signals obtained from animals with different time post-surgery were analyzed. Our results show that as the time post-lesion increases both frequency parameters decrease. Changes in the PDS have been detected since 3 weeks post-lesion and significant differences were found between different conditions. In addition morphological analysis revealed a transition from a symmetrical to an asymmetrical morphology.

Motor Systems

P199.-Testing the effects of Yerba mate (Ilex paraguariensis) in a Drosophila model of Parkinson´s disease

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Parkinson's disease (PD) is the second worldwide neurodegenerative disorder in prevalence. Its origin is unknown, but its pathophysiological characteristic is the progressive degeneration of dopamine-releasing neurons (nDA) of the Substantia nigra pars compacta. Recently, an epidemiological study conducted in Argentina revealed that the consumption of yerba mate (YM) has an inverse association with the risk of developing PD (Gatto, 2015). Furthermore, we have found that YM extract induces a strong neuroprotective effect on dopaminergic neurons *in vitro* (Bernardi, 2019). Given these promising evidences, we aimed to test the potential neuroprotective effect of YM in an in vivo model of PD. We have chosen a model where the WT human alpha synuclein is over-expressed panneuronally in Drosophila melanogaster, which induces several motor deficits and has been widely used to study PD. To reach our goal, we have set up the administration of YM to flies, characterized the a-Syn model in our hands and produced preliminary behavioral and molecular data. In this poster we will show the feeding method, as well as preliminary results that suggest that YM administration produces an improvement of motor coordination in PD flies. Even if our preliminary results are encouraging, further work is still necessary to demonstrate a neuroprotective role of YM in vivo.

Motor Systems

P200.-Rhythmic synchronous effects in cortical neurons songbirds
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*Presenting author: **Santiago Boari,** santiagoboari@gmail.com*

How vocal communication signals are represented in the cortex is a major challenge for behavioral neuroscience. Beyond a descriptive code, it is relevant to unveil the dynamical mechanism responsible for the neural representation of auditory stimuli. In this work, we report evidence of synchronous neural activity in a cortical region of songbirds, in response to auditory playbacks of the bird's own song. The rhythmic features of the song of canaries (Serinus canaria) allowed us to show that this synchronization was locked to defined frequencies of the behavior. We recorded neurons in a brain region where sensorimotor integration occurs. Here, we show that these neurons are activated at specific temporal instances of the song and are phase-locked to oscillations of the Local Field Potentials. These effects occur at different depths within the studied cortical region and also in both brain hemispheres, indicating long-range synchronization across the bird's brain.

Motor Systems

P201.-Local field potential in cortical avian nucleus supports a circular model for birdsong production
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Song production in oscine birds is a key topic in motor control of a complex behaviour. It is fundamental for advancing research in other aspects of birdsong such as learning and memory. Song is produced when the output of a dedicated set of nuclei drives the vocal organ and the respiratory system to interact in precise biomechanical motor gestures. Telencephalic nucleus HVC (used as a proper name) plays a key role in the production of motor commands that drive the periphery, and the neural code it uses is still under debate. In canaries (Serinus canaria), the motor gestures of the periphery during vocalization have been studied in detail. A recent population model of the neural system makes specific predictions about the timing of the sparse activity in HVC during the production of motor gestures. While single-unit isolation can be labour intensive, recording the local-field potential is straightforward and provides information about synchronized activity of neurons. Following our studies of single-unit activity in nucleus HVC of singing canaries, we continued to use tetrodes to record LFP chronically during song. We found oscillations in the LFP locked to syllable production rate occurring reliably during a session. Also, troughs in the LFP signal are associated with relevant features of the syllable being produced. These findings advance our current understanding of this system and support the predictions from the neural population model.

Motor Systems

P202.-Sex-frailty differences in aging mice: neuropathologies and therapeutic projections

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In the present study, we evaluate possible frailty predictors in older mice in a sex-specific manner. We also observe the effects of IGF-1 gene therapy and its correlation with the expression of these frailty and emotionality. In order to evaluate frailty index we employed two different approaches, we perform a frailty assessment through a 31-Item Clinical Frailty Index and through a Performance-Based Eight-Item Frailty Index. Both indexes are in concordance to evaluate sex differences, but they do not correlate when evaluating IGF-1 therapy effects. Moreover, to reduced test-to-test variability for measures of dependent variables, in this aging model we compared open field results across studies of sex and treatment evaluation using z-score normalization. Our data show that regular open field parameters submitted to Z-score normalization analysis could be a useful tool to identify sex differences in aging mice after growth factors therapies. Considering that gender is a factor that influences the incidence and/or nature of all major complex diseases, our work is one of the first ones that compares the use of different frailty indices calculations to identify sex differences and therapy efficiency in aging models, specifically by the use of noninvasive therapeutical strategies.

Motor Systems

P203.-Significant instances in motor gestures of different songbird species

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The nervous system representation of a motor program is an open problem for most behaviors. In birdsong production, it has been proposed that some special temporal instances, linked to significant aspects of the motor gestures used to generate the song, are preferentially represented in the cortex. In this work, we compute these temporal instances for two species, and report which of them is better suited to test the proposed coding (as well as alternative models) against data.

Motor Systems

P204.-Deletion of NMDA receptors in cholinergic neurons increases L-Dopa induced dyskinesia
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Parkinson's disease (PD) is caused by the degeneration of the nigrostriatal dopaminergic projection to the striatum, a key nucleus for the selection of motor programs. L-dopa therapy is the best symptomatic treatment, however, abnormal movements (L-dopa-induced dyskinesia-LID) emerge with disease progression and long term treatment. Striatal cholinergic interneurons are key modulators of striatal circuits, are hyperexcitable in animal models of PD and more excitable in animals with LID. NMDA glutamate receptors (NMDAR) have been linked to LID; in fact the non-competitive NMDAR antagonist amantadine is used as an antidyskinetic agent. Here we used the Cre-loxP system to generate mice with a deletion of the NMDAR1 subunit (NR1) in cells expressing choline acetyltransferase (ChAT.NR1-KO) to ask if NMDAR in cholinergic cells contribute to LID development. Behavioral assessment of ChAT.NR1-KO mice showed no motor impairment compared with control mice. Moreover, the parkinsonian phenotype induced by unilateral nigrostriatal lesion with 6-OHDA was not modified by NR1 deletion. Mice were then treated with increasing doses of L-dopa for three weeks and LID were scored. Unexpectedly, ChAT.NR1-KO mice showed more severe LID compared with control mice, at low doses of L-dopa only, suggesting that NMDAR in cholinergic neurons reduce LID sensitization during repeated L-dopa administration. Overall, the data suggest that NMDAR located on cholinergic neurons have antidyskinetic effects.

Neural Circuit Physiology

P205.-Long-lasting remodeling of inhibitory networks by hippocampal adult neurogenesis
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The dentate gyrus of the hippocampus is dominated by a strong GABAergic tone that maintains sparse levels of activity. Adult neurogenesis disrupts this balance through the continuous addition of new granule cells (GCs) that display high excitability while develop and connect within the preexisting host circuit. The dynamics of the connectivity map for developing GCs in the local inhibitory networks remains unknown. We used optogenetics to study afferent and efferent synaptogenesis between new GCs and GABAergic interneurons expressing parvalbumin (PV-INs) and somatostatin (SST-INs). Inputs from PV-INs targeted the soma and remained immature until they grew abruptly in >4-week-old GCs. This transition was accelerated by exposure to an enriched

environment. Inputs from SST-INs were dendritic and developed slowly until reaching maturity by 8 weeks. Synaptic outputs from GCs onto PV-INs matured faster than those onto SST-INs but also required several weeks. In the mature dentate network, PV-INs exerted an efficient control of GC spiking and were involved in both feedforward and feedback loops, a mechanism that would favor lateral inhibition and sparse coding. Our results reveal a long-lasting transition where adult-born neurons remain poorly coupled to inhibition, which might enable a parallel streaming channel from the entorhinal cortex to CA3 pyramidal cells.

Neural Circuit Physiology

P206.-Analysis of neuron firing rates and covariance during rapid kindling

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Rapid kindling (RK) has emerged as an alternative method of the traditional kindling to reproduce temporal lobe epilepsy in rats in a shorter period; and thus, allows studying different aspect of the epilepsy. Previously, we showed that neuron single-unit activity (SUA) modify their firing patterns between basal and ictal periods and that seizure duration increases as the kindling progress. Now, we aimed to describe the underlying changes produced by the successive stimulation that may explain the epileptogenesis of the RK model. Male Wistar rats were implanted with a bipolar macroelectrode into the right ventral hippocampus and eight microwires into the right dorsal hippocampus. Treated rats received twelve stimulations per day through the macroelectrode (50-150 µA; 20 Hz; 500 µs; 10 sec) along 3 days, while sham rats were implanted but received no stimulation during the protocol. Whole electrical activity was recorded continuously during the experiment. All the data registered was processed and different SUA was identified by sorting. Neuronal firing rate (FR) and the covariance (CV) of the interspike interval were calculated for each SUA. The analysis of FR and CV along the protocol showed that there is significative increases in FR per days followed by a progressive increase in the CV. Future studies will be focused on determine how these parameters are involved in the progression of the epileptogenesis in this model.

Neural Circuit Physiology

P207.-Early ethanol preexposure modifies expression of the 5HT2A receptor promoting long-term breathing plasticity in neonate rats

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EtOH's effects upon respiration are attributed to central respiratory network disruptions, especially in the medullary serotonin (5HT) system. 5HT2A/2C receptors are involved in the reduction of the phrenic nerve

activity and breathing depression. We hypothesize that early EtOH preexposure alters neonatal respiration through the 5HT system´s plasticity. Here, we evaluated breathing rates and the relative expression of 5HT 2A and 2C receptors in the brainstem as a function of EtOH preexposure in neonates. Pups received i.g administrations of 2.0 or 0.0g/kg EtOH at postnatal days (PD) 3, 5 and 7. At PD 9, breathing frequencies were recorded under normoxia or hypoxia. Brainstems were collected to quantified relative mRNA expression of 5HT 2A and 2C receptors by qPCR. Under normoxia, EtOH preexposed pups (preEtOH) exhibited high 5HT2A expression levels and breathing depressions. An opposite phenomenon was observed in preEtOH pups tested under hypoxia. An exacerbated hyperventilation associated with low 5HT2A expression levels was found. No significant differences were found in 5HT2C expression levels. These results together with our previous findings that show changes in the raphe obscurus activation patterns, suggest that a brief EtOH preexposure is enough to induce 5HT system's plasticity, disturbing neonatal breathing. The 5HT components mismatch may be associated with breathing disruptions commonly observed in human neonates, such as Sudden Infant Death Syndrome.

Neural Circuit Physiology

P208.-Neuronal correlates for the timely execution of actions in the dorsal striatum

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The selection and the appropriate execution of sequences of movements is essential to survival. Striatal activity has been shown to signal the initiation and termination of behavior and it is also involved in the selection of future actions. Here we studied the neuronal activity of the dorsal striatum of adult rats that were trained to obtain water by emitting a sequence of 8 licks following a visual cue. Trials were self-initiated by the animal by entering into the nose-poke following a 2.5 s inter-trial interval (ITI). We found a modulation of the neuronal activity related to different events in the task such as the the execution of the action sequence, reward delivery and at the boundaries of the trials (nosepoke entry and exit). In particular, firing rate modulation previous to the beginning of the trials was larger for longer waiting times. This anticipatory activity did not merely reflect elapsed time nor the motor plan to be executed so, to assess if it was related to reward expectancy, rats were trained to initiate trials in a restricted time-window (ITI 2.5-5s). Results show thatactivity modulation for long waiting times differed between both versions of the task: when the ITI was long and had no reward associated to it, the amplitude of the modulation decayed, whereas rewarded long ITIs had an increasing anticipatory activity. We hypothesize this striatal activity reflects the animals' subjective valuation of timing and is key for the timely execution of actions.

Neural Circuit Physiology

P209.-Adult born dentate granule cells evoke CA3 activity with a gain that increases along maturation

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Hippocampal granule cells (GCs) are among the few neurons that are born throughout mammalian lifespan. It has been shown that young adult born GCs (4 weeks old) are transiently hyperplastic and excitable compared to

mature ones (8 weeks old). While their inputs are well characterized, only a few studies address the maturation of GCs outputs. Here we aim to investigate the influence of developing adult born GCs on CA3, its main target. We hypothesize that evoked activity in CA3 reflects transient properties of young GCs. To explore this possibility, we performed optical stimulation of a cohort of adult born GCs expressing channelrhodopsin-2 in awake behaving mice while recording neuronal activity in CA3. We used different frequencies of stimulation at variable laser intensities to stimulate young and mature GCs. We found that mature GCs recruit more CA3 single unit activity, with frequency dependent facilitation. Evoked local field potentials followed a similar pattern. Interestingly, a small subset of putative pyramidal CA3 cells presented significantly high spiking levels as long as 50 ms after the light pulse. Only mature GCs were able to evoke this sustained activity. Is this persistent excitability caused by attractor dynamics? Do adult born neurons reshape de architecture of recurrent CA3 networks? These results open new challenges regarding the function of adult hippocampal neurogenesis and mnemonic networks dynamics dependent on the neurogenic niche.

Neural Circuit Physiology

P210.-Lower density of perisomatic GABAergic boutons containing α1 subunit and Excitation/Inhibition imbalance in a mouse model of schizophrenia

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Schizophrenia in characterized by cognitive symptoms that are present before the onset of psychosis. Cognitive processes correlate with synchronous activity, which at the neuronal level is represented by membrane potential oscillations, critical for neuron firing and produced by excitatory and inhibitory inputs. Importantly the excitation (E) is balanced by inhibition (I), i.e. when E increases, I proportionally increases and is maintained in each cycle in a wide range of synaptic conductance. Parvalbumin interneuron (PVI) activity seems crucial for the E/I balance, and also, PV dysfunction may lead to cognitive deficits. Thus, PVI function deficits may produce a new E/I steady state or an altered dynamic range of E/I balance, and thus alter the circuit function. We used a model of PVI dysfunction by selectively ablating the NMDAR in corticolimbic PVIs to test if the E/I balance in the adult mPFC is altered by a PV dysfunction early. The results show that KO mice show altered E/I balance at the functional connectivity level that can be compensated only under low network activity. Here we propose to find a structural correlate to the E/I changes in the KO mice by estimating the GABA synapses in the mPFC.We found that mPFC neurons of KO mice have less α1 subunit perisomatic GABA synapses, whereas there is no change in those containing the α2 subunit or PV. Finally, we found differences in the frequency of I inputs vs the number of perisomatic α1 GABAergic synapses correlation.

Neural Circuit Physiology

P211.-Exploring the influence of higher order brain regions on the piriform cortex neuronal activity

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The Piriform cortex (PC), the main region of the olfactory cortex, receives afferent (bottom-up) sensory inputs from the olfactory bulb (OB) and extensive (top-down) inputs from higher-order areas such as the basolateral

amygdala (BLA) and the lateral entorhinal cortex (LEC). To understand the contribution of the BLA and LEC to the processing of odors we study their functional connectivity to the posterior PC (pPC). We infected the BLA and the LEC with adeno-associated virus to express channelrhodopsin (ChR2-AAV) in either excitatory neurons (under CamKIIa promoter) or inhibitory Parvalbumin interneurons (using PV-Cre mice). We recorded then, in acute brain slices, postsynaptic currents and spiking in different principal neurons of the pPC in response to photostimulation. We found that both excitatory and inhibitory long range projections coming from the BLA synapse preferentially onto pyramidal neurons of the deep layers of pPC and do not contact semilunar neurons of the superficial layer. Moreover, we discover that inputs from both BLA and LEC can modulate the output of pPC neurons in response to stimulation of OB afferents. The LEC and BLA inputs could provide contextual and valence information associated to odors. To investigate the role of those regions in the processing of odors in vivo, we are conducting experiments to photoinactivate them alternatively during an associative odor-context-reward task and evaluate the effect of that manipulation on the behavior.

Neural Circuit Physiology

P212.-Cortical spiking activity entrainment with beta oscillations is enhanced after nigrostriatal degeneration and when L-DOPA effects have worn off

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Abnormal involuntary movements known as L-DOPA-induced dyskinesia (LID) are a common complication in Parkinson's disease (PD) after prolonged treatment with L-DOPA, which is the gold standard medication. Little is known about the oscillatory activity associated with LID, especially in the motor cortex (MC). However recent studies show that exaggerated beta activity (15–35 Hz) who emerge in the basal ganglia after nigrostriatal degeneration, correlate with motor impairment in PD and can be suppressed by LID. Our previous characterization in MC disclosed a similar pattern, with an increased number, duration and power of beta events. Interestingly this pattern was reverted during the acute effect of L-DOPA, but reappeared when L-DOPA effects have worn off. Here we sought to identify cortical neuronal populations related to this rhythm. We performed recordings of single unit activity by means of high density electrodes in primary MC of parkinsonian mice before and after L-DOPA regime that induced LID. We found an increased mean firing rate in both conditions. Also, phase preference of spiking activity to beta oscillations was higher in lesioned than in sham animals. This pattern was present both in putative pyramidal neurons and interneurons. These results reveal a better entrainment of neuronal activity with beta oscillations in the parkinsonian condition, which is not reversed by chronic L-DOPA administration, and could explain the increased beta power previously observed.

Neural Circuit Physiology

P213.-Physiological significance of the KCNQ4-mediated M-current in the pedunculopontine nucleus of the reticular activating system

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The pedunculopontine nucleus (PPN) is part of the reticular activating system (RAS) which is associated with sleep regulation. The PPN has cholinergic and non-cholinergic neurons. A hallmark of the PPN-cholinergic neurons is the M-current, a slowly activating, non-inactivating voltage-gated potassium current. KCNQ2 to 5 subunit alone or in combination are responsible for the M-current. Our aim was to investigate the contribution of the KCNQ4 subunit to PPN neuronal function. We used a transgenic mouse model for KCNQ4 (knock-out (KO)) and one with fluorescent-labeled cholinergic neurons (tdTomatoStop+ChAT::Cre). We analyzed KCNQ4 expression by real-time PCR and its localization using immunofluorescence. We also studied the M-current by electrophysiology on brain slices, the contribution of KCNQ4 to neuronal activity and its influence on circadian rhythm. We found a weak mRNA expression of KCNQ4 in PPN and the protein was located only on cholinergic neurons of the external limits of the nucleus. M-current was present in most of cholinergic neurons in WT animals, but absent in 40% of them in the KO ones. These last also exhibited behavioral alterations in the activity cycles showing a 5-hour increase and a higher sensitivity to changes in the light/darkness cycles. In summary, we found that only a subpopulation of PPN cholinergic neurons have KCNQ4-dependent M-current and this subunit contributes to modulate the circadian rhythm through the activity of the RAS system.

Neurochemistry and Neuropharmacology

P214.-Protective effects of imidazolium salts in C. elegans models of stress and neurodegeneration

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In this work, using an established model in biomedical research, the nematode C. elegans, we synthesized imidazolium salts and performed a screening to analyze their ability to improve oxidative stress (OS) resistance. We identified a derivate, 1-Mesithyl-3-(3-sulfonatopropyl)imidazolium (MSI), that enhances animal resistance to OS. To delineate MSI roles, we split this work into two goals: i) to describe MSI action mechanisms and, ii) to evaluate MSI role in neurodegenerative models. To gain insight into its mechanism of action, we evaluated MSI ability to activate DAF-16 (FOXO in vertebrates), a transcription factor relevant for cytoprotective defense mechanisms. Unexpectedly, our experiments revealed that MSI stress protection was not dependent on DAF-16. These results support the idea that other transcription factors (such as SKN-1 (Nrf-2 in vertebrates), HSF-1), could be involved in MSI protection. The second goal is held by the theory that links OS to aging and neurodegeneration. We are currently evaluating if MSI increases lifespan, healthspan, and improves biological markers of neurodegeneration in a C. elegans model of Alzheimer disease. This strain expresses Aβ1-42 in muscle and shows age-dependent protein aggregation and paralysis. Our preliminary results show that MSI delays paralysis in this strain. Additional research is needed to underpin the protective role of MSI and to determine if these effects can be extrapolated in other neurodegenerative scenarios.

Neurochemistry and Neuropharmacology

P215.-Neuroprotective effect of melatonin loaded in ethylcellulose nanoparticles applied topically in a retinal degeneration model in rabbits

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During the development of different ocular pathologies, such as glaucoma, oxidative stress becomes the main cause of cellular damage. The antioxidant capacity of the cell is insufficient to protect the retinal ganglion cells (RGCs). Therefore, the exogenous administration of antioxidant agents is a promising strategy to inhibit some of the steps involved in the death of retinal cells. Melatonin (ME) has been described as being an effective antioxidant in the retina with direct and indirect free radical scavenging properties. This project describes the elaboration of nanocapsules (NCECMEs) containing ME, and includes the formulation, physicochemical characterization, in vitro drug release, transcorneal permeation studies and an in vivo study of irritation. The neuroprotective effect of ME was also evaluated using the induced retinal degeneration (RD) model.In vitro ME release (1 and 2 mg/mL) from NCECMEs was found to be slower than ME solution. However, ex vivo assays demonstrated a higher permeation, attributable to the extended residence time of NCECMEs and also an ME effect on the membrane at low concentrations, leading to an increase in drug absorption. NCECMEs appeared to be more efficient for RGC protection, compared to ME solutions, against induced RD model, as indicated by damage indicators such as the apoptotic index (AI) and retina integrity.

Neurochemistry and Neuropharmacology

P216.-Flavone derivatives with broad range of therapeutic effects for Alzheimer´s disease
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Alzheimer´s disease (AD) is a multifactorial neurodegenerative disorder. Flavonoids are known for their wide range of CNS-related activities. We aim to develop novel multitarget drugs for AD. We screened a library of synthetic flavonoid derivatives combining different substitutions. All of them showed capacity to bind to the benzodiazepine binding site of the GABAA receptor. We tested them for their capacity to inhibit AChE and BChE (enzymes targeted by AD medications) and MAO A & B (enzymes are altered in AD brain). Most of the flavonoid compounds showed a capacity to inhibit MAO B (IC50 values ranging within 2-22 µM) and also 4 of them inhibited BChE (IC50 for values ranging: 58-68 µM -human enzyme-; 9-19 µM -mice plasma enzyme. Then we assessed in vivo the effect of the administration of a compound which combines the most active substitutions (COMB) in mice. In a novel object recognition task, the previous i.p. injection of COMB (10 mg/kg), 15 min before (1 mg/kg) scopolamine i.p injection (pharmacological AD model) (given 20 min prior training session) prevented mice from scopolamine STM impairment and led mice to express an LTM. No significant effect was observed after the i.p. administration of COMB (1-10 mg/kg) neither in the Plus Maze, Hole-Board nor Locomotor activity tests (given 30 min prior each behavioural assay). COMB seems to be a promising compound with broad range of therapeutic effects for AD patients.

Neurochemistry and Neuropharmacology

P217.-Enriched environment induces neuroprotection against visual disfunctions within experimental glaucoma in rats

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Glaucoma is a leading cause of blindness, characterized by retinal ganglion cell (RGC) loss and optic nerve (ON) damage. Increased intraocular pressure (IOP) is the most accepted risk factor for glaucomatous neuropathy, however many patients with successful IOP control continue to lose vision. Enriched environment (EE) consists of a manipulation in which animals are exposed to complex conditions through adaptations in the physical and social environment. The aim of this work was to analyze whether the exposure to EE is able to prevent glaucomatous damage. Adult male Wistar rats received 30% of chondroitin sulfate in the anterior chamber of one eye and vehicle in the contralateral eye, once a week, and were housed in standard environment (SE) or EE for 10 weeks. Animals were subjected to functional (flash visual evoked potentials (VEPs)), and histological analysis. EE housing which did not affect IOP, prevented the disfunction in VEPs as well as the anterograde transport to visual areas and RGC loss (assessed by Brn3a-immunoreactivity). The axon number was also preserved by the exposure to EE. Moreover, EE housing prevented the decrease in the immunoreactivity for myelin basic protein and luxol fast blue staining in the ON, as well as the increase in Iba1 (a microglia/macrophage marker) positive area in the retina and ON. These results suggest that the EE housing protects the visual pathway against retina and optic nerve damage induced by experimental glaucoma.

Neurochemistry and Neuropharmacology

P218.-CB1 receptor agonism potentiated stress-induced enhancement of extracellular glutamate in nucleus accumbens core after extinction of cocaine-conditioned place preference

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Neurochemistry and Neuropharmacology

P219.-The blockade of low affinity neurotensin receptor alters mitochondrial bioenergetics and the triade NMDA receptor, PSD-95 and nNOS proteins

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In previous work we have shown the impairment of nitric oxide (NO) production and mitochondrial alterations after the blockade of low affinity neurotensin receptor (NTS2) by levocabastine. A functional interaction between neuronal nitric oxide synthase (nNOS) and NMDA receptor through assembly with PSD-95 protein has been described. Male Wistar rats were i.p. injected with levocabastine (50 μg/kg) or saline and sacrificed 18 hours later. Brain cortex crude mitochondrial fractions and synaptosomal membranes were isolated by differential and sucrose gradient centrifugation, respectively. Levocabastine administration decreased 31% and 34% state 3 respiratory rates assayed with malate-glutamate and succinate, respectively, and 21% themitochondrial membrane potential ($p<0.05$). In addition, ATP production rate decreased 57% using malate-glutamate as substrates ($p<0.01$). Also, the in vitro addition of 1 μM levocabastine significantly decreased all mitochondrial function parameters. Western blot assays showed that protein expression of nNOS, PSD-95, NMDA NR2B subunit and β-actin after levocabastine administration were respectively 56, 72, 34 and 45% lower than in controls ($p<0.05$). Results suggest that the blockade of NTS2 receptor by levocabastine leads to an important mitochondrial dysfunction. Impaired bioenergetics and ATP depletion could alter the assembly between nNOS, PSD-95 and NMDA NR2B subunit proteins leading to NO syntheses inhibition at synapses.

Neurochemistry and Neuropharmacology

P220.-Argentine valerians: Potential effects on CNS targets related to Alzheimer disease

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Alzheimer's disease (AD) is a neurodegenerative disease whose pathophysiology is associated with an abnormal accumulation of proteins (β-amyloid, tau), oxidative stress, alterations in neurotransmitter levels(mainly acetylcholine), among others. Our country harbors several thousands of plant species, which lack scientific information although many of them are used in folk medicine. Our hypothesis is that native plants have unexplored compounds with multiple biological activities on CNS. Herein we present a study of hydroalcoholic extracts of 5 Argentine valerians (underground parts): V. carnosa, V. macrorhiza, V. clarionifolia, V. effusa y V. ferax, y V. officinalis (Caprifoliaceae). These extracts were evaluated in vitro for the presence of AChE & BChE inhibitors (mice brain homogenate/plasma); inhibition of β amyloid peptide aggregation and antioxidant properties (DPPH assay). Although all extracts were able to inhibit both AChE (IC50 between 1.1-12.1 mg/ml) and BChE (IC50 between 0.0018 -1.46 mg/ml), the most promising results were obtained for BChE, where V. clarionifolia showed the highest inhibition. Futhermore, all valerians (0.1 mg/ml) inhibited β amyloid aggregation, V. effusa and V. clarionifolia were the most active. Also, a direct relationship between the antioxidant capacity and the phenol content was observed. Our study is an important contribution for the discovery of unkwown native herbal products with CNS effects to develop novel therapeutical agents.

Neurochemistry and Neuropharmacology

P221.-Early noise exposure can induce short and long term changes on reactive oxygen species (ROS) levels and catalase activity (CAT) in developing rat hippocampus that can be prevented through housing in an enriched environment during adolescence

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We have shown that early noise exposure can induce hippocampus (HC)-related behavioral, molecular and histological alterations and that housing animals in an enriched environment (EE) can be used as a preventive strategy. However, as data of HC-oxidative state have not been obtained yet, the aim of this work was to test whether noise can affect ROS levels and catalase activity in the developing rat HC as well as to assess the effectiveness of the housing in an EE. Male rats of 7 and 15 postnatal days (PND) were exposed to noise (95-97 dB, 2h) for one (N1) or five (N5) consecutive days. After weaning, rats were transferred to EE or standard cages for one or two weeks. Levels of ROS and CAT activity were tested at different times after noise exposure: short term (ST: 30min, 1 and 24h) and long term (LT: PND28 and 35). At ST, results showed a decrease in ROS levels in all groups except for PND7N1 rats, whereas, no changes were found in CAT activity. When evaluated at LT, rats exposed at PND7 showed a decrease in both ROS and CAT at PND28, whereas an increase in ROS and a decrease in CAT were found at PND35. Rats exposed at PND15 showed a decrease in CAT only at PND35. Finally, EE was effective in preventing these changes only at PND35. These findings suggest that noise exposure can differently affect HC oxidative state, according to the age of exposure, which can be detected even in adolescence. In addition, EE could be an effective strategy to prevent these changes.

Neurochemistry and Neuropharmacology

P222.-Evidence of the role of cyclin dependent kinase 5 in DAT expression and functioning

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Abnormal dopaminergic system functioning has been related to a broad of psychiatry disorders such as Parkinson, Schizophrenia, Attention Deficit Hyperactivity Disorder, among others. One of the key proteins that regulate Dopamine (DA) transmission efficiency is Cyclin dependent kinase 5 (Cdk5). In this sense, mice lacking Cdk5 activator, p35 (p35KO) mimic the symptoms and shared ADHD dopaminergic abnormalities. Thereby, p35KO mice display an increased DA striatal content, an augmented DA synthesis pathway and decreased DA metabolism. Given that, DA neurotransmission is modulated by Dopamine Transporter (DAT), which mediates the reuptake of DA, we studied DAT surface expression and uptake capacity in striatum of p35KO and WT control mice. Through biotinylation assays, we demonstrated that p35KO mice exhibit reduced DAT surface expression in striatal synaptosomes compared to WT mice, although total DAT levels do not differ between genotypes. In agreement with these results, amperometric measurements of DA reuptake, using a nanostructured electrochemical sensor based on a glassy carbon electrode modified with carbon nanotube as analytical platform, showed that p35KO mice present a decrease of DA uptake compared with WT animals.

These results suggest a critical role of Cdk5 in DAT expression and functioning and provide new insights of the regulation of DA neurotransmission in neuropsychiatric disorders.

Neurochemistry and Neuropharmacology

P223.-Implementation of an axotomy paradigm in Drosophila wings to study the role of FKBP2 in neurodegeneration

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FKBP51 and FKBP52 are immunophilins that bind immunosuppressive drugs such as FK506. FKBP51/52 are abundant in the nervous system, are not related to immunosuppression and their function at the neuronal level is unclear. FK506 protects and regenerates the nervous system upon several types of injuries. Recently, we found that FK506 promotes in vitro neurodifferentiation and regeneration of murine neurons in a FKBP52-dependent manner. However, mechanisms involved in this effect have not been elucidated and in vivo studies are necessary. Here, we implemented a model of axotomy in Drosophila wing to investigate the role of FKBP52 in neuronal degeneration. In this model, glial cells or neurons expressing fluorescent proteins can be easily visualized over time and changes after nerve injury can be recorded. Using this model, we observed that 2 dpa (days post axotomy) there is an increase in pigment spots in the veins, a sign of inflammatory processes. 7 dpa there is an increase in intensity and discontinuous fluorescence patterns in glia cells. Finally, 2 and 7 dpa, the L1 nerve thickness is reduced and there is a fluorescence discontinuity and reduction of glutamatergic axons. Toxicity studies showed that treatments with FK506 for 3 days at concentrations ranging from 0.01 µM to 1 mM do not alter the survival of adult flies.This model will allow us to examine the effect of FK506 in vivo and the underlying mechanisms of FKBP52 in nerve injury.

Neurochemistry and Neuropharmacology

P224.-Participation of cofilin in the sensitization between chronic stress and cocaine in nucleus accumbens core

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It has been demonstrated that exposure to stress predisposes to developing substance use disorders. Our previous results have shown long-term changes in proteins that regulate actin cytoskeleton in the nucleus

accumbens core (NAc) during the expression of cross-sensitization between stress and cocaine. We described modifications in levels of cofilin phosphorylation along with an increase in the PSD size and an enhancement in AMPAR surface expression in NAc. Here, we evaluate the influence of cofilin, a direct regulator of actin cytoskeleton remodeling, during stress-induced sensitization to cocaine. For this purpose, we have generated a lentivirus containing an interference RNA specific to suppress cofilin expression (shRNAcofilin) and explore its function and changes associated with long-term plasticity in NAc. Thus, chronically pre-stressed male rats were administered intra-NAc with shRNAcofilin, 20 days before a challenge with cocaine, when behavioral sensitization was evaluated. Additionally, we examined changes in the AMPAR surface expression and spine morphology, thought to contribute to the expression of cocaine sensitization. Our findings reveal that the inhibition of cofilin, is sufficient to prevent stress-induced sensitization to cocaine and impedes the GluR1 surface enhancement in NAc, in pre-stressed animals. These findings constitute a molecular mechanism influencing actin cytoskeleton remodeling in the NAc during cross sensitization between stress and cocaine.

Neurochemistry and Neuropharmacology

P225.-Behavioral and pharmacological challenges unmask ketamine long-term alterations: AT1 receptors role

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Ketamine administration, a validated animal model of schizophrenia, resembles some of the behavioral symptoms and structural alterations of the pathology. Our group has evidences supporting Angiotensin II AT1 receptors (AT1-R) role in behavioral, neuroinflammatory and neurochemical responses in amphetamine and ketamine models of schizophrenia. The present work aims to study astrogliosis and neuronal survival in somatosensory cortex (S1) in ketamine treated animals and the AT1-R involvement. In addition, hot plate test was used as behavioral output of S1. Methods: Male Wistar rats (250-320g) were administered with AT1-R antagonist Candesartan/vehicle (3mg/kg p.o., day1-6) and Ketamine/saline (30mg/kg i.p., day 6-10). Hot plate test was performed under naive conditions (day 0) and after 14 days of withdrawal of ketamine treatment. On day 25, glial reactivity (GFAP) and neuronal survival (cresyl violet) were evaluated at basal condition and after ketamine challenge (15mg/kg i.p.; -24hs). Data were analyzed by factorial ANOVA. Results: Ketamine treated animals displayed an increased thermal nociception. Ketamine challenge increased neuronal death, without astrogliosis, that was prevented by AT1-R blockade. At basal conditions, no changes were observed. Conclusion: ketamine-induced alterations were prevented by AT1-R blockade, supporting the protective effects of AT1-R blockers described for several brain diseases.

Neurochemistry and Neuropharmacology

P226.-Behavioral and molecular modulation of the stressed glutamatergic synapse by fasudil, a Rho-kinase inhibitor with antidepressant potential

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Chronic stress modulates brain glutamatergic systems, namely the hippocampus, that may result in depressive and anxiety disorders. Antidepressants trigger molecular and morphological changes at the glutamatergic synapse, including variations in the levels of AMPA and NMDA receptors, resulting in improved plasticity and behavioral outcomes. Considering that Rho-kinase inhibition by fasudil has antidepressant-like actions in rodents, we evaluated whether fasudil elicits changes in AMPA and NMDA subunits levels in hippocampal synaptic fraction of stressed rats and if it prevents stress-induced behavioral impairments. Adult male Sprague-Dawley rats were treated with fasudil (ip., 10 mg/kg/day) or vehicle for 18 days and some animals were daily restrained (2.5 hr/day from day 4 to 18). 24-hr after treatments, elevated plus maze, object location task and western blotting of hippocampal synaptoneurosomes were performed. We found that fasudil prevented stress-induced anxiety-like behavior and loss of novelty preference as indicated by open arms spent time and discrimination index values, respectively. Furthermore, we observed that fasudil reduced synaptic GluA1 and NR2B levels in stressed animals, while it increased synaptic GluA1 and GluA2 levels in unstressed animals. Our results support the notion that fasudil triggers molecular modulations of the glutamatergic synapse under a stress paradigm preventing behavioral impairments, thus supporting its antidepressant potential.

Neurochemistry and Neuropharmacology

P227.-Inhibition of NFkB pathway in Nucleus Accumbens core prevents stress-induced cross-sensitization to cocaine

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Neurochemistry and Neuropharmacology

P228.-Potential uses of new human erythropoietin (hEPO)-derivatives for the treatment of neurodegenerative diseases

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Neurodegenerative diseases are characterized by the progressive degeneration of the structure and function of the central or peripheral nervous system. The treatments available for these pathologies are non-effective, so new neuroprotective agents are in continue development. In this area, EPO plays a key role because of its neuroprotective activity and capacity to repair cell damage in the brain. Nevertheless, its hematopoietic activity (HA) must be considered as a side effect. We developed new hyper-N-glycosylated hEPO-derivatives. We introduced N-glycosylation potential sites in regions of hEPO essentials for the HA activity but not for the neuroprotective and neuroplastic action. We developed three EPO variants with high purity level (89%), showing an apparent molecular mass higher than EPO and a superior number of acidic isoforms as a result of the increased glycosylation degree. The in vitro and the in vivo HA of each EPO variant was abolished ($p<0.001$). Nevertheless, all of them preserved the neuroprotective and neuroplastic activity. The EPO variants prevented

staurosporine-induced apoptosis ($p<0.001$) and promoted neuritogenesis ($p<0.05$ and $p<0.001$), filopodia density ($p<0.05$ and $p<0.001$) and synapsis formation ($p<0.01$ and $p<0.01$). Consequently, those hEPO-derivaties result excellent candidates to treat patients or prevent people with genetic predisposition to develop neurodegeneration in which enhancing neuroplasticity and/or neuroprotection have a beneficial effect.

Neurochemistry and Neuropharmacology

P229.-Sciatic nerve recovery after a chronic constriction injury model using EPA/DHA-concentrate fish oil

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The aim of this work was to assess the preventive effect of an EPA/DHA-concentrate fish oil on Neuropatic Pain development and regenerative features of ciatic nerve in rats. In the present study, rats with chronic constriction injury (CCI) of the sciatic nerve and sham-operated ones received omega-3 fatty acids (0.36 or 0.72 g/kg/day, oral) or saline solution for 21 days, with thermal hyperalgesia and mechanical allodynia being assessed before and 3, 7, 14 and 21 days after injury. Omega-3 fatty acids (0.72 g/kg) reversed thermal hyperalgesia and significantly reduced mechanical allodynia. In addition, ω-3 treatment (0.72 g/kg) promoted the recovery of the Sciatic Functional Index as well as restored axonal density and morphology, without the formation of neuroma in the injured sciatic nerves after 21 days. We conclude that the omega-3 fatty acids administration relieves thermal hyperalgesia and mechanical allodynia effectively and also enhances the recovery process in rats with CCI of the sciatic nerve. These findings might contribute to new therapeutic approaches including omega-3 fatty acids in neuropathic pain treatment.

Neurochemistry and Neuropharmacology

P230.-Impact of microglial depletion through colony-stimulating factor 1 receptor inhibition on demyelination and neurodegeneration in a chronic cuprizone-induced demyelination model

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Cuprizone (CPZ)-induced demyelination is widely used as a multiple sclerosis (MS) model to study de/remyelination processes. Microglia (MG) participate in demyelination and neurodegeneration processes and are physiologically dependent on colony-stimulating factor 1 receptor (CSF-1R) signaling. Therefore, we aimed to evaluate the effects of CSF-1R inhibitor BLZ945 on demyelination and neuroregeneration in mice submitted to chronic CPZ demyelination. Mice were fed either control or CPZ (0.2% w/w) chow for 12 weeks and orally

gavaged vehicle or BLZ (200 mg/kg/day) from the 2nd week of CPZ treatment (C, BLZ, CPZ and CPZ+BLZ). BLZ treatment induced a reduction in the number of MG in all structures evaluated and attenuated demyelination in corpus callosum (CC), striatum (ST), fimbria (F), external splenium CC (ESCC) and cerebellum (CE). Positive amino-cupric-silver (ACS) staining was prominent in axons traversing the ST and fibers throughout the CC, ESCC, F and CE in CPZ and CPZ+BLZ, and even more prominent in ST and CC in CPZ+BLZ. Axonal degeneration was accompanied by terminal axonal ovoids characteristic of inflammatory demyelination. ACS staining was hardly observed in axonal terminal puncta at synaptic sites or neuron bodies. These results indicate that neurodegeneration does not exclusively result from demyelination and that MG depletion could prevent demyelination but also exacerbate axonal degeneration. These data could be transferred to the treatment of progressive MS.

Neuroendocrinology and Neuroimmunology

P231.-Characterization of Ghrelin-responsive neurons of the lateral hypothalamic area

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Lateral hypothalamic area (LHA) is a brain region involved in the control of feeding, energy balance and motivated behavior, among other functions. LHA neurons express high levels of the ghrelin receptor (or, growth hormone secretagogue receptor, GHSR). Ghrelin is a stomach-derived peptide that regulates diverse functions exclusively via GHSR. In this study, we characterized GHSR neurons of the LHA. First, we mapped the distribution of GHSR neurons of the LHA using mice in which the enhanced green fluorescent protein (eGFP) is expressed under the control of the GHSR promoter (GHSR-eGFP mice). Then, we assessed the ability of GHSR neurons of the LHA to sense central or peripheral ghrelin by using a fluorescent ghrelin analog, and found that only centrally administered ghrelin reaches LHA cells. Also, we found that GHSR neurons of the LHA increase the level of the marker of neuronal activation c-Fos in response to centrally injected ghrelin and fail to increase c-Fos in response to systemically injected ghrelin. We also found that GHSR neurons of the LHA do not express melanin concentrating hormone, orexin or the marker of GABA cells Gad65. Moreover, intra-LHA ghrelin administration increases food intake and locomotor activity. Thus, current data suggest that GHSR neurons of the LHA, whose phenotype remains unknown, could regulate some behavioral functions independently of plasma ghrelin levels.

Neuroendocrinology and Neuroimmunology

P232.-Characterization of Ghrelin/GHSR system role in a 60% caloric restriction protocol

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The hormone ghrelin is essential to cope energy deficit conditions, when plasma ghrelin levels increase and activate central functions that help to maintain glycaemia and increase appetite. These ghrelin actions are mainly mediated by the agouti-related protein (AgRP)-producing neurons of the arcuate nucleus (ARCAgRP neurons). Here, we hypothesized that up-regulation of the ghrelin system in calorie restricted (CR) mice promotes morphological remodeling of the ARCAgRP neurons that, in turn, would impact on the compensatory refeeding response after the CR period. First, we characterized a 60% caloric restriction protocol in wild-type

(WT) mice. We found that CR WT mice lost 25% of their body weight after 5-day of CR, and that displayed a 5-day compensatory hyperphagia after refeeding. As compared to ad libitum fed mice, CR mice showed 1) higher plasma ghrelin levels, 2) higher density of AgRP+ fibers in several brain areas and 3) a matched increase of the levels of the marker of neuronal activation c-Fos in those brain areas. To test if these effects require the presence of the ghrelin receptor (GHSR), we studied CR GHSR-deficient mice. We found that CR GHSR-deficient mice lost ~25% of BW after 5-day 60% CR, similar as seen in WT mice, but showed a significantly smaller compensatory hyperphagia after refeeding. Thus, we conclude that ghrelin/GHSR system is involved in the regulation of the compensatory hyperphagia in CR mice.

Neuroendocrinology and Neuroimmunology

P233.-Dissecting the immune response in the CNS: astrocytic response to interaction with leukocytes

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The old paradigm on CNS immune privilege has been reformulated and a role for peripheral immune system in CNS immune processes is accepted, although not completely understood. The view of astrocytes physiology has also shifted. There is a general consensus in that astrocyte population shows high degree of heterogeneity, as does its response to different pathological contexts. A more detailed comprehension of the response of CNS local immune cells to its peripheral counterparts is crucial for a global understanding of neuropathological processes. In the present work we used an in vitro co-culture model to study astrocytic response. To achieve this, we cocultured rat primary glial cells with acutely obtained leukocytes from naïve or rats exposed to brain ischemia which models stroke. Our results showed that when enriched astrocytic culture (95-98% GFAP+) contacted leukocytes (from either naïve or ischemic rats) there were no significant alterations in GFAP immunoreactivity reactivity or morphological phenotype. However, astrocytic cellular retraction and reorganization was evident, and scar-like structures were seen when leukocytes contacted mixed glial primary cultures that include microglia. Moreover, fixed leukocyte also induced these scar-like structures, indicating that surface molecules present in leukocytes might be enough to cause them. Using leukocytes from ischemic rats did not show significant differences.

Neuroendocrinology and Neuroimmunology

P234.-Neural modulation of systemic stress response requires the insulin like-peptide INS-3 in C. elegans

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Perpetuation of the flight response inhibits defensive cytoprotective mechanisms, leading to early onset of age-related disorders from invertebrates to mammals.We have recently shown that, in C. elegans, the flight response induces neuronal release of Tyramine (TA, invertebrate analog of adrenaline), that stimulates the adrenergic-like receptor TYRA-3 in the intestine. This leads to the activation of the DAF-2/Insulin/IGF-1 pathway in non-intestinal cells and the inhibition of cytoprotective mechanisms. However, the signals that link the activation of TYRA-3 in the intestine with the DAF-2 insulin receptor in other tissues is unknown. We, therefore,

performed a screening of Insulin like-peptides expressed in the intestine by RNAi and identified that lack of ins-3 improves resistance to oxidative and thermal stress. This resistant phenotype cannot be reversed by exogenous TA and it is mediated, at least partially, by DAF-16/FOXO. Moreover, by using genetics we found that tyra-3 and ins-3 act in the same pathway. In addition, we found that only the intestinal rescue of ins-3 null mutants was able to restore the resistance to wild-type levels. We propose that INS-3 could be the signal molecule that connects the intestine, where TA receptor is expressed, with distal tissues. Given the high degree of conservation of fundamental mechanisms, this work can contribute to the understanding of neurohormonal coordination of stress responses in animals.

Neuroendocrinology and Neuroimmunology

P235.-Increased pro-inflammatory response in a mouse model of neurodevelopmental disorder

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Rett Syndrome (RTT) is a pervasive developmental disorder caused by mutations in methyl-CpG binding protein 2 (MeCP2), a ubiquitous transcriptional regulator. The goal of our project is to evaluate the role of MeCP2 in immune responses in vivo, using an animal model of Multiple Sclerosis (EAE) as an autoimmune challenge and in vitro, using bone marrow derived macrophages (BMDM). Male MeCP2 WT and MT mice, were immunized with MOG 35-55 peptide, scored daily for EAE symptoms and sacrificed at 12 dpi (acute stage) or at 30 dpi (chronic stage). We found that MT-EAE mice showed an accelerated onset of the disease and more severe clinical scores, accompanied by increased infiltration of lymphocytes in spinal cord. Also, we detected a sustained higher expression of TNFα and IFNγ in spinal cords from MT-EAE animals during chronic stage compared to WT. Next, we assessed the response of BMDM from WT and MT mice stimulated with either pro- or anti- inflammatory stimuli. M1-polarized BMDM-MT showed increased expression of TNFα, while M2-polarized BMDM-MT, presented lower levels of FIZZ1, IL10, and CD206 compared to BMDM-WT. Also, independently of the stimuli, BMDM-MT showed higher levels of superoxide production. Thus, MeCP2 mutation appears to bias the response toward a pro-inflammatory profile.Overall, our results suggest that MeCP2 has an active role in maintaining the immune homeostasis in vivo and regulating the immune response in vitro.

Sensory Systems

P236.-Non image forming visual system alterations induced by experimental opticneuritis: therapeutic effect of melatonin

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Optic neuritis (ON) is an inflammatory condition of the optic nerve (OpN), which leads to retinal ganglion cell (RGC) loss. A subset of RGCs expressing the photopigment melanopsin regulates non-image-forming (NIF) visual system functions such as pupillary light reflex (PLR) and circadian rhythms. ON can be induced by a single microinjection of bacterial lipopolysaccharide (LPS) into the OpN. We analyzed the effect of ON on the NIF visual

system, and the effect of melatonin on NIF visual system alterations induced by ON. OpNs from male Wistar rats received vehicle or LPS, and one group of animals received a subcutaneous pellet of melatonin. LPS significantly decreased blue light-evoked PLR, and induced a misconnection between the retina and the suprachiasmatic nuclei (assessed by ex vivo magnetic resonance images). LPS induced a significant decrease in Brn3a(+) RGCs, but not in melanopsin(+) RGC number. A bilateral injection of LPS significantly increased the light (but not dark) phase locomotor activity, rhythm periodicity, and activity offset time. Melatonin prevented the decrease in blue light-evoked PLR, and locomotor activity rhythm alterations induced by ON. These results support that ON provoked alterations of the circadian physiology, and that melatonin protected the NIF visual system function against ON.

Sensory Systems

P237.-A novel behavioural task for rodents: olfactory discrimination in a visual context

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The ability to learn that a sensory stimulus signals a reward or punishment is one of the brain's function most critical for adaptation and survival. How animals integrate information about a learned sensory stimuli with the spatial context and the animal´s internal state is not completely understood. Here we developed a learning paradigm to assess the influence of spatial context on the association of odor-reward. Water-restricted mice were trained to perform a GO/NO GO discrimination task in which the animal learns to drink water or not depending on the visual context in which the odor is presented. In a head-fixed state, animals arrive to different spatial contexts by running in a virtual reality environment. We show that animals reached criterion within a few sessions. Licking response developed readily, shifted from being constant throughout the trial to being adjusted to the reward zone. Locomotion speed and inhalation rate also changed, depending on trial types. We observed that mice learn to discriminate odors faster than visual contexts, suggesting a difference in stimuli salience. Since proper response to odor help animals to adapt to changing environments, we studied flexibility of the behavior. We carried out a reversal learning protocol by changingthe rewarded odor. Results showed that reversing the behavior took 3-4 sessions. This behavioral task is suited to probing the neural basis of spatial context modulation of an olfactory-based behavior.

Sensory Systems

P238.-Noise exposure triggers changes in synaptic function in mammalian hair cells

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Noise-induced hearing loss has gained relevance as one of the most important sources of hearing loss. It has been shown that acoustic trauma (AT) producing only transient auditory threshold shifts also produces long-term reductions in the number of synapses between inner hair cells (IHCs) and afferent neurons. Here we intend to address if the capacity of IHCs to release neurotransmitter is altered after AT.

Mice were exposed to loud sounds for 1 hour, and evaluated one day later for cochlear function. Exocytosis in IHC was tested by measuring changes in membrane capacitance (ΔCm) triggered by step depolarizations. IHCs from exposed WT mice displayed larger ΔCm jumps compared to unexposed IHCs using short pulses at different voltages. Larger differences were found at the maximal release points in the curve. Also, exposed IHCs showed augmented ΔCm with pulses of extended duration, longer than 100 ms. No differences in calcium entry between exposed and control cells were observed for any of the applied depolarizations. To determine if this potentiated release was triggered by glutamate released during AT and acting retrogradely, we made use of the vesicular transporter vGluT3 knock-out (KO) mouse. Exposed KO showed reduced ΔCm compared to controls, in contrast to what was observed in WT mice. These results suggest that AT enhances vesicle release in IHC, possibly by accelerating vesicle recruitment, and this would be dependent upon the intense glutamate release.

Sensory Systems

P239.-Postnatal stress exposure impairs visual function in adult mice

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The early postnatal period is characterized by extensive neuronal plasticity, synaptic organization, and remodeling. High neuroplasticity renders the brain sensitive to the remodeling effects induced by environmental factors, such as exposure to adversity. Long-lasting effects of early life stress (ELS) have been intensively studied in central areas of the brain, but ELS influence on vision remains to be explored. Our aim was to assess ELS effects on visual function in adult mice. For that purpose, newborn C57BL/6J mice were exposed to maternal separation during lactation and were weaned at postnatal day 17 (MSEW). Visual function was evaluated in adult mice by electrophysiological and behavioral tests. MSEW-exposed pups showed less body weight and opened eyes after control pups. MSEW-exposed mice showed a lower negative scotopic threshold response and photopic negative response compared to control mice, suggesting a diminished function of the inner retina. Visual acuity was evaluated through a looming test with varying intensity stimuli. MSEW animals needed higher intensities of the looming stimulus to respond similarly to control animals, suggesting a lower visual acuity. Finally, MSEW animals showed less side preference in a cliff avoidance test when compared to control animals, suggesting impaired depth perception. Altogether, our data indicate that ELS may be detrimental to visual function in adult mice.

Sensory Systems

P240.-Unravelling the molecular components of the cholinergic efferent system in zebrafish lateral line

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Zebrafish (z) lateral line (LL) is a mechanosensory system that consists of hair cells (HC) innervated by afferent neurons that transmit information to the CNS and by efferent neurons that make direct contact with hair cells.

LL HC share many characteristics with those in vertebrate inner ear, namely efferent stimulation to these systems leads to similar effects, suggesting the existence of similar synaptic mechanisms. It is known that the alpha9 alpha10 (α9α10) nicotinic receptor (nAChR) mediates efferent transmission in the cochlea, however this information is lacking for zLL. RNAseq studies have recently shown that α9 is differentially expressed both in LL and inner-ear HCs. We have cloned zα9, expressed it in X. laevis oocytes and performed two-electrode voltage-clamp recordings. α9 homomeric nAChR are activated by Ach, and reversibly blocked by α-Bungarotoxin (α-Btx). α9 nAChRs exhibit high calcium (Ca2+) permeability and large desensitization rates. To study the properties of the native zLL nAChR, we performed in vivo Ca2+ imaging in transgenic zebrafish larvae that express a genetically encoded Ca2+ sensor specifically in HC. We measured Ca2+ entering HC through Cav1.3a channels during mechanical stimulation as a proxy of its electrical state. ACh reduces evoked Ca+2 influx and this effect is blocked by α-Btx. These results support the idea that a nAChR composed of the α9 subunit could be mediating transmission at the efferent synapse of zLL.

Sensory Systems

P241.-The medial efferent system during development of the auditory pathway

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The auditory system of many mammals develops after birth. It has been described that before the onset of hearing inner hair cells (IHCs) of the cochlea are innervated by neurons of the afferent system and transiently by neurons of the medial olivocochlear system. During this period, IHC exhibit periodic depolarization patterns, that produce the release of glutamate. These events induce stereotyped bursts of action potentials that are transmitted to the auditory circuits in the brain and promote physiological maturation, and the proper establishment of the tonotopic map. The transient efferent innervation to IHCs of the cochlea has been proposed as a modulator of this activity. In this work we sought to understand the function of this transient synapse during the beginning of hearing. We used a previously reported genetically modified mice carrying an α9 cholinergic receptor subunit point mutation that leads to enhanced responses to medial olivocochlear activity. First, we analyze the onset of hearing and we found that these knock-in gain of function animals start to hear a day before than wild types, which means that the efferent system might be involved in cochlear development. Second, we observed that the maturation of the auditory system is a process that occurs from the periphery towards the higher nuclei. Finally, we evidenced that afferent synapse formation begins as a multiple innervation. At the onset of hearing, a "prune" and refinement of these synapses occurs.

Sensory Systems

P242.-Melatonin as a therapeutic strategy against the alterations in the non-image forming visual system induced by experimental glaucoma

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Glaucoma is a major cause of blindness, characterized by retinal ganglion cell (RGC) and optic nerve axon loss. A subset of RGCs expressing the photopigment melanopsin regulates non-image-forming (NIF) visual system functions, such as pupillary light reflex (PLR) and circadian rhythms. Glaucoma induces significant alterations in the NIF visual system. Our aim was to analyze the effect of melatonin on the NIF visual system alterations induced by glaucoma. Experimental glaucoma was induced in male Wistar rats by weekly intracameral injections of chondroitin sulfate (CS) for 10 weeks, while the contralateral eye received vehicle injections. One group of animals received a subcutaneous pellet of melatonin at 6 weeks of CS-treatment. Melatonin prevented the decrease in the blue and white light- evoked PLR, in melanopsin(+) RGC number, and in the anterograde transport from the retina to the olivary pretectal nucleus and the suprachiasmatic nucleus (SCN) induced by experimental glaucoma. Bilateral glaucoma significantly increased the light phase locomotor activity, and rhythm periodicity, whereas melatonin restored the locomotor activity daily rhythm. A significant decrease in light-induced c-Fos expression in the SCN was observed in glaucomatous animals, which was not evident in melatonin-treated animals. These results support the therapeutic role of melatonin against the NIF visual system alterations induced by glaucoma.

Sensory Systems

P243.-Melatonin protects the retinal pigmentary epithelium and photoreceptor damage within experimental non-exudative age-related macular denegeration

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Non-exudative age-related macular degeneration (NE-AMD), the main cause of blindness in the elderly, is characterized by retinal pigment epithelium (RPE) and photoreceptors (PR) atrophy exclusively circumscribed to the macula. There are no effective therapeutic strategies that can prevent or delay the NE-AMD. It has been suggested that RPE oxidative damage plays an important role in NE-AMD pathogenesis. Melatonin is an effective antioxidant and has proven effects within several retinal neurodegenerative disorders. We have developed a NE-AMD model induced by superior cervical ganglionectomy (SCGx) in adult C57BL/6J mice, which reproduces NE-AMD hallmarks exclusively circumscribed to the central temporal RPE/outer retina, a region comparable to the human macula. In this context, the aim of this work was analyzing the effect of melatonin on the alterations induced by SCGx. Melatonin prevented the visual function, the decrease in RPE melanin content and RPE65-inmunorreactivity, and the RPE and PR ultrastructural alterations at 10 weeks post-SCGx. Moreover, melatonin prevented the decrease in mitochondrial mass (MitoTrackerRed (+) area, and levels of specific mitochondrial proteins) as well as the increase in RPE and PR oxidative stress markers at 6 weeks post-SCGx. These findings suggest that melatonin could be a possible novel therapy for treat the dAMD.

Sensory Systems

P244.-Configural or elemental representation of complex odor stimuli in the olfactory system of Drosophila melanogaster

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The olfactory system is an excellent model to study how sensory stimuli are detected and processed in the brain. Odor molecules bind to receptor proteins expressed in the olfactory receptor neurons (ORNs), which project to the antennal lobe (AL). Here, all ORNs that express the same receptor converge into glomeruli and make contact with projection neurons (PNs), which constitute the output of the AL, and with local neurons (LNs) that form a network of lateral interactions. Due to the spatial organization of the input to the AL, each odor is encoded as a combination of coactivated glomeruli. The response elicited by a mixture of odors differs from the summation of the activity elicited by the elements that constitute the mixture. It is thought that this non-elemental representation accounts for the perception of the mixture as a novel stimulus, different from the components. Here we study the representation of pure odors and its mixture in the AL of Drosophila melanogaster flies. We perform optical calcium imaging at the level of the AL by expressing GCaMP6 in the PNs. We measure the representation of pure odors and mixtures. The differences among the patterns of activity elicited by the mixture and those expected on the basis of the activity elicited by pure components reveals the action of the local network which is based mainly on GABAergic inhibitions. Future studies are directed to measure the representation of the mixture while interfering with the action of the LNs.

Sensory Systems

P245.-Measuring vision using innate behaviors in rats with intact orimpaired visual functions

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The aim of this work was to develop a method for measuring vision in rats. Male Wistar rats were placed in a rectangular arena with a computer monitor placed on top displaying a gray screen. After 5 min of habituation, in which animals commonly displayed exploratory postures (rearing on the hind legs and sniffing), a visual stimulus was triggered. The looming stimulus was a black/gray disk rapidly widening to 50 degrees of visual angle in 250 ms. The black/grey contrast was manipulated to assess changes in response to contrast magnitude. After a latency in a range of ms, the stimulus provoked a response consisting in only three different behaviors: freezing, head bobbing, and upward rearing. The relative amount of these responses changed with contrast magnitude range. A linear correlation between the cumulative frequency of responding animals and the black/gray contrast magnitude was found. Arbitrarily, visual acuity was defined as the contrast magnitude at which 50% of animals responded. Animals submitted to unilateral ischemia (induced by increasing intraocular pressure to 120 mm Hg for 40 min), optic neuritis (induced by the microinjection of LPS into the optic nerve) or glaucoma (induced by chronic intracameral injections of chondroitin sulfate) showed a significantly less visual acuity than control animals. Therefore, the innate response of aerial predator avoidance could be used as a reliable method to assess visual functions in rats.

Sensory Systems

P246.-Perceptual quality and internal representation of odors mixtures is tuned by experience

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Animals are able to sense their environment and generate an internal representation of it. This ability is important to, among other things, perceive and locate food sources. In this context, sensory mechanisms and behavior evoked by different stimuli are studied to understand how animals detect and integrate environmental information. A requirement in the detection and processing of this information is the ability to discriminate between stimuli that, although they are physically similar, may have different meanings, and that of generalizing between stimuli that, although physically different, may have the same meaning. In many cases this ability is innate, however, in many others it is determined by experience. Previous studies showed that appetitive experience with an odorant changes the internal representation of a mixture that contains it, where the activity pattern evoked by the mixture is more similar to the representation of the rewarded component and less to that of the novel component. It has been interpreted that those changes would favor the perception of the rewarded component, which could otherwise be occluded by the perception of the mixture as an odor distinct to its components. In the present study we evaluate if those changes do have a real impact in the way an odor mixture is perceived. We confirm that previous experience with the pure components affect the perceptual quality of the mixture in close parallel to the changes in its internal representation.

Sensory Systems

P247.-Sensory preconditioning and perceptual learning in honey bees Apis mellifera
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The ability to learn and recognize an object is a fundamental ability of the nervous system. Animals must be able to learn which elements of the sensory input belong together and constitute an object. To address this in honey bees we use an olfactory preconditioning protocol which involves three phases. The first one is the stimulation with a binary odor mixture. In the second one, one of the components of the mixture is reinforced according to a Pavlovian conditioning protocol. Finally, we test if the component that was part of the mixture but was not used during the conditioning phase elicits the learned response. The ability of the non-rewarded odor to elicit the conditioned response serves as evidence that both odors have been associated during the first phase. In the present study we address if, as for classical appetitive learning, a single exposure event induces a short-term memory of the binary mixture as an object, and if multiple exposure trials endow a long-term memory of the object. Results obtained so far indicate a weak effect of sensory preconditioning in the short-term and no long-term memory. A possible interpretation is that the binary mixture elicits the perception of a stimulus that is too different from the components and thus, no generalization between components and mixture is possible. We are testing now if shortly desynchronizing the odors during stimulation with the mixture, improves segregation of the components and thus sensory-preconditioning.

Sensory Systems

P248.-Resveratrol prevents oxaliplatin-induced neuronal injury and allodynia through anti-oxidant and anti-inflammatory mechanisms

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Chemotherapy-induced peripheral neuropathic pain (CIPNP) is a frequent and devastating side effect of cancer therapy. No preventative strategies are available. We evaluated the use of resveratrol (RESV) in the prevention of CIPNP and the mechanisms involved. Male rats were injected with oxaliplatin (OXA) and received RESV or vehicle in their drinking water, starting before chemotherapy and thereafter. Mechanical and thermal allodynia and the expression of anti-oxidant, pro-inflammatory and neuronal injury markers were evaluated at lumbar dorsal root ganglia (DRGs) and spinal cord (SC). Animals receiving OXA showed a decrease in paw mechanical and thermal thresholds ($p<0.01$ vs CTL from day 1 and thereafter), while those receiving OXA+RESV showed patterns of response similar to those detected in CTL animals ($p>0.05$ at every time point). A significant increase in the mRNA levels of ATF3, NFkb and TNF was detected in the DRGs of OXA animals, while an upregulation of c-fos, Nrf2, NFkb and TNF was observed in the dorsal SC ($p<0.05$ vs CTL in all cases). RESV administration was able to prevent ATF3, c-fos, NFkb and TNF upregulation ($p>0.05$ vs CTL in all cases), while inducing an increase in the expression of Nrf2 and SIRT1 ($p<0.01$ vs CTL, $p<0.01$ vs OXA). These results show that RESV systemic administration upregulates anti-oxidant mediators while suppressing pro-inflammatory parameters, thus preventing OXA-induced neuronal damage and neuropathic pain.

Sensory Systems

P249.-Coding of Behavioral Context in the Olfactory Cortex

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Sensory representations are typically thought as neuronal activity patterns that encode physical attributes of the outside world. However, both internal state and behavioral relevance of a stimulus may modulate neuronal coding in sensory cortical areas. To study this phenomenon, we developed a behavioral task in a virtual reality environment in which head-fixed mice learn that an odor is rewarded when presented in a specific spatial context, and recorded neuronal activity in piriform cortex (PC). We find neurons not only responding to odors, but also to visual contexts and to water reward, indicating that the PC encodes information about relevant aspects of the task. Moreover, using Principal Components Analysis (PCA) of population activity dynamics, we show that population trajectories evolving thorough time can discriminate aspects of different trial types. Through Generalized Linear Models (GLMs), we further dissect the contribution of different variables to the modulation of PC activity at the level of individual trials. We show that, after learning the task, animal position in the virtual environment has considerable impact on PC responses. Furthermore, we found that variables related to both sensory and behavioral aspects of the task (e.g., odor, context, reward, licking, sniffing rate and running speed) differently modulate PC activity, suggesting that the PC may use information from other brain areas to adapt odor processing depending on experience and behavior.

Sensory Systems

P250.-A two-step detection system for defensive responses in arthropods

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Luminance changes and object motion detection provides essential cues for a wide variety of behaviors such as mate, prey or predator detection. In our lab we have been studying the neural circuits involved in detecting threatening visual stimuli in a highly visual crab. In this work we started studying changes in the animal's heart rate as a readoutof sensory perception. By presenting a visual danger stimulus, animals responded by slowing their heart rate. There is a high correlation between this response and the intensity of stimulation. Detailed analyzes through electrocardiograms showed a heart rate dynamic in which two cardiac response phases can be distinguished. Phase I is an early response, temporarily located in the first half of the stimulation interval. Phase II, instead, is a later response, apparently supported by greater information integration. By using two stimulation protocols we adapted both phases differentially. Our results indicate that heart rate activity can be modulated, at least, by two visual detection systems. The biological purpose of such modulation, as well as the concerted execution of other behavioral responses, will be discussed at the poster.

Synaptic Transmission and Excitability

P251.-GABA modulation of olivocochlear efferent neurotransmission

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During development, inner hair cells (IHCs) in the mammalian cochlea are unresponsive to acoustic stimuli but instead present intrinsic electrical activity, crucial for the normal development of the auditory pathway. During this same period, neurons originating from the medial olivocochlear complex (MOC) transiently innervate IHCs. This innervation is mediated by acetylcholine (ACh), activating nicotinic receptors assembled by α9 and α10 subunits and is responsible for controlling IHC excitability during this period. Even though this is a cholinergic synapse, previous evidence indicates the presence of abundant GABA and presynaptic GABAB receptors. Moreover, the application of GABAB receptors agonists can reduce ACh release. To determine the source of GABA in the MOC – IHC synapse, transgenic mice expressing channelrodhopsin (ChR2) in GABAergic fibers were used. Preliminary results indicate that ChR2 activation by light did not elicit any measurable synaptic response in IHC per se, but produced a transient potentiation of cholinergic synaptic responses (when coupled with an electrical stimulation) in 10/28 cases. In addition, immunohistochemistry techniques were used to characterize GABA innervation. On the other hand, to further understand the mechanisms of GABA modulation we used calcium imaging techniques that allowed us to estimate activity at a single synapse level. Altogether these results suggest that ACh might be released from fibers that have a GABAergic identity.

Synaptic Transmission and Excitability

P252.-Intracellular modulation of α7 ionotropic and metabotropic functions by tyrosine phosphorylation

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The α7 receptor is a nicotinic receptor present in neuronal and non-neuronal cells. α7 acts as a ligand-gated ion channel and as a metabotropic receptor. We investigated the role of tyrosine phosphorylation of the intracellular domain (ICD) in the dual ionotropic/metabotropic receptor function. Single-channel recordings from HEK cells expressing α7 showed that channel activity appears as brief isolated openings and episodes of few openings in quick succession (bursts). Exposure to an inhibitor of Src family kinases (PP2) increased the frequency and duration of bursts while preincubation with an inhibitor of tyrosine phosphatases had the opposite effect. Co-expression of α7 and an inactive Src kinase also increased burst duration. A mutant α7 lacking tyrosine phosphorylation sites in the ICD showed longer burst durations and insensitivity to PP2, thus recapitulating the effects of phosphorylation inhibition on wild-type α7. Cells exposed to the specific α7 agonist (PNU-282987) showed an increase of ERK1/2 phosphorylation, which was abolished by exposure to a tyrosine kinase inhibitor. PNU-282987 did not trigger ERK phosphorylation in cells expressing the mutant receptor lacking tyrosine residues or co-expressing α7 and α7-ICD domain. Our results indicate that dephosphorylation positively modulates ionotropic α7 activity in a way compatible with decreased desensitization, and that the phosphorylated state of α7-ICD plays a role in metabotropic receptor responses.

Synaptic Transmission and Excitability

P253.-Histamine-enhanced ASIC mediated currents contribute to anterior cingulate cortex long-term potentiation

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Acid-sensing ion channels (ASICs) are H+-gated channels belonging to the ENaC/Deg superfamily that are involved in synaptic transmission and in neurodegenerative diseases. During synaptic transmission, acidification of the synaptic cleft due to the co-release of neurotransmitter and H+ from synaptic vesicles activates ASIC channels in mice. We used slices from the anterior cingulate cortex (ACC) of P30-60 postnatal mice to evoke glutamatergic AMPA receptor-mediated excitatory postsynaptic currents (EPSCs), recorded in whole-cell patch-clamp at layer I pyramidal neurons. After blocking AMPA, NMDA, GABA and glycine receptors, we detected ASIC mediated synaptic currents (ASIC-SCs) sensitive to ASIC-1a inhibitor psalmotoxin-1.ASIC-SCs were enhanced by the neuromodulator histamine, which specifically modulates homomeric ASIC-1a channels, as well as by corticosterone. Long-term potentiation (LTP) is a major type of long-lasting synaptic plasticity and is associated with learning, memory, development and neuropathic pain. Neurons in the ACC play critical roles in chronic pain. LTP was induced by theta burst stimulation (TBS) of the callosal afferents. Extracellular field EPSP and whole-cell patch-clamped EPSC recordings demonstrated that ASIC-SCs contribute to ACC LTP induction. Stimulated by a TBS below threshold, glutamatergic synapses undergo LTP by the potentiating effect of histamine on ASIC channels, which is prevented by previous incubation with psalmotoxin-1.

Synaptic Transmission and Excitability

P254.-Evaluation of synaptic Ca2+ signals of opposite sign in cochlear outer hair cells

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Cochlear outer hair cells (OHCs) are responsible for controlling the gain of auditory inputs by means of a unique cellular property that allows them to alter their shape in response to voltage changes. This function is modulated by a cholinergic input coming from the brainstem and mediated by the Ca2+ permeable α9α10 nicotinic receptor. Ca2+ influx through this receptor is coupled to the activation of Ca2+-dependent K+ channels within a very narrow domain limited by a near-membrane postsynaptic cistern. Thus, cholinergic activity hyperpolarizes the OHC and inhibits cochlear amplification. We aimed to determine the magnitude and spread of synaptic Ca2+ signals and the role of the synaptic cisterns using simultaneous electrophysiological recordings and Ca2+ imaging techniques. Electrical stimulation of axons revealed single efferent Ca2+ entry sites. The amplitude of the signal correlated with that of the evoked postsynaptic currents and it was dependent on efferent stimulation frequency. Moreover, pharmacological manipulations suggested a possible role for Ca2+ extrusion mechanisms in Ca2+ signal termination. Finally, OHC depolarizations activated voltage-gated Ca2+ channels producing local Ca2+ levels similar to those obtained by the cholinergic input. Since OHCs present afferent glutamatergic innervation and presynaptic active zones are closely positioned to efferent postsynaptic cisterns, crosstalk between these two synapses will be discussed.

Synaptic Transmission and Excitability

P255.-Activity dependent excitatory/inhibitory imbalance in the medial prefrontal cortex pyramidal neuron inputs in a parvalbumin positive neuron dysfunction mouse model.

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In the medial Prefrontal Cortex (mPFC), cognitive processes require a balanced interplay of interneurons and pyramidal neurons (PN). In particular parvalbumin interneurons (PV) seem to be required for the balance of excitatory and inhibitory (E/I) inputs that produce membrane potential subthreshold oscillations. Importantly neurodevelopmental illnesses like schizophrenia, show dysfunction in the PV activity that may alter the PN physiology and the E/I balance. Here we focused on the effects of PV dysfunction on the membrane properties, morphology and E/I balance of PNs in the mPFC using a mouse line where the NMDAR is eliminated from corticolimbical PV neurons early on, showing molecular and behavioral markers resembling schizophrenia. Firstly, we found a reduced and less complex dendritic tree and an increased excitability in PNs of KO mice. Furthermore whereas the E/I balance was not altered in the spontaneous activity of acute slices, the miniature events displayed a reduced IPSC and normal EPSC frequencies, increasing the E/I balance. And finally, whole cell voltage clamp recordings under higher activity levels in the prefrontal cortex, as found during in vivo experiments, show an altered E/I balance in the KO mice. These results indicate that circuit alterations during early neurodevelopment imprint an altered functional connectivity that may be compensated only under low levels of circuit activity reducing the dynamic range of E/I balance control.

Synaptic Transmission and Excitability

P256.-Functional plasticity of cortico-striatal neurons of the Anterior Cingulate Cortex during the transition to chronic pain

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Neuropathic pain (NP) is a debilitating neurological condition of high clinical relevance. At the cellular level, the increased sensitivity to pain is mediated by changes in neuronal function along the entire nociceptive pathway. The Anterior Cingular Cortex (ACC) is essential for the perception of the affective dimension of pain and is hyperactive in patients suffering from chronic pain and in animal models of NP. Recent studies in patients suggest that abnormal recruitment of basal ganglia (BG) structures, involved in the motivational evaluation of stimuli and actions, may facilitate the persistence of pain. However, there is so far little evidence on how BG pathways are affected during chronic pain. In this context, our hypothesis is that projections from the ACC to dorsomedial striatum could serve as a direct route for spreading out pathological cortical activity to BG. To gain insight on this, here we evaluated if enhanced ACC excitability during NP engages neurons that project to the striatum. Combining neuronal identification with fluorescent retrograde tracers and ex-vivo electrophysiological recordings (brain slices), we studied the dynamics of synaptic properties and intrinsic excitability of ACC cortico-striatal neurons during the transition to chronic pain in a rodent model of NP. Our preliminary results suggest that neuronal plasticity in the ACC is cell-type specific and evolves during pain chronification.