SAN2021
EBOOK

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PROGRAM

	OCT 18	OCT 19	OCT 20	OCT 21	OCT 22
09:00 11:00		**SYMPOSIA** Tue-S1 to Tue-S3: Alba, Bisig, Biurrun&Coronel	**OC SESSIONS** (OC1- OC4)	**SYMPOSIA** Thu-S7 to Thu-S9: Kaczer, Pallares, Setton	**YOUNG INVESTIGATORS TALKS** Fri-YIT4 to Fri-YIT5
11:00 11:30	**Opening Words** (Cancela) "EDUARDO DE ROBERTIS" **LECTURE** **Rita Raisman-Vozari** (Chairs: Ferrario, Antonelli, Stahl)	Biobreak			**E-SOCIAL** **Scientific publications: Journals and editorial policies** (Rayes, Zorrila, Ceriani) **Gender inequities and inequalities around the world** (Antonelli, Murta)
11:30 12:30		**PLENARY LECTURE** **Peter Kalivas** (Chairs: Cancela, Pacchioni, Pautassi, Coll)	**PLENARY LECTURE** **Andrea Nistri** (Mazzone, Unsain)	**PLENARY LECTURE** **Maria Dolores Ledesma** (Sodero, Adamo)	
12:30 13:00			Biobreak		
13:00 14:00			**E-SOCIAL** **Co-authorship network structure and gender inequalities of the Argentine neuroscientific community** (Bekinstein, Fernandez)		
14:00 16:00	**E-POSTER SESSIONS** (PS1 - PS3)	**E-POSTER SESSIONS** (PS4 - PS7)	**SYMPOSIA** Wed-S4 to Wed-S6: Rela, Echeveste&Samengo, Wilson&Moyano	**E-POSTER SESSIONS** (PS8 - PS10)	**SYMPOSIA** Fri-S10 to Fri-S11: Durand, Monteleone&Brocco
16:00 16:30			Biobreak		
16:30 17:30	**YOUNG INVESTIGATORS TALKS** Mon-YIT1 to Mon-YIT3	**PLENARY LECTURE** **Silvia Bunge** (Andreau, Brocco)	**PLENARY LECTURE** **Vivian Budnik** (Rayes, Contin)	**PLENARY LECTURE** **M. Laura Feltri** (Setton, López)	"RANWELL CAPUTTO" LECTURE **Carlos Dotti** (Chairs: Cancela, Guido, Sodero, Fernández)
17:30 18:00		Biobreak			
18:00 19:30	**E-SOCIAL** **Navigating the gray areas to do Neuroscience** (Mazzone, Rayes)	**E-SOCIAL** **Socio-environmental modulation of cognitive processes** (Fernandez Larrosa, Andreau)	**E-SOCIAL** **Looking for training abroad? Tips for international interviews** (Zorrilla, Beckwith, Fernandez)	**ASAMBLEA SAN** Elecciones	**E-SOCIAL** **Neuro-cine** (Ferrario, Avale)

PLENARY LECTURES

"Eduardo De Robertis" Lecture

An old drug for new treatment: Neuroprotective effects of doxycycline in Parkinson Disease

Rita Raisman-Vozari
Experimental Therapeutics of Parkinson's Disease Paris Brain Institute
Sorbonne Université UM75

Parkinson's disease (PD) is a neurodegenerative disorder for which only symptomatic treatments, such as levodopa and dopamine agonists are available. These drugs ameliorate motor symptoms however they could induce adverse side effects. The mechanism that drives the chronic progression of PD remains elusive. Among the proposed underlying pathophysiological mechanisms, aggregation of α-synuclein, neuroinflammation, and oxidative stress, have been credited to contribute to neuronal loss. Thus, to efficiently modify the course of neurodegeneration in PD, an ideal drug should be capable of interfering with α-synuclein aggregation, halting the generation of toxic species, and inhibiting neuroinflammatory processes. Doxycycline (DOX), a wide-spectrum antibiotic that belongs to the group of the tetracyclines has been suggested by our international research team for repurposing in PD, due to the fact that it has anti-inflammatory and antioxidant properties and mitigates the loss of dopaminergic neurons in an animal model of PD. In addition, we showed that DOX inhibit the pathological aggregation of α-synuclein by reshaping toxic oligomeric species towards strains with reduced toxicity, seeding capacity, and propensity to form amyloid fibril and attenuates the production of mitochondrial-derived reactive oxygen species. During my talk, I will provide strong evidence that doxycycline treatment may be an effective strategy against PD and other synucleinopathies.

Signals from the 4th Dimension Regulate Drug Relapse

Peter Kalivas
Department of Neuroscience, Medical University of So Carolina, Charleston USA

Treatments for psychiatric disorders, such as substance use and stress disorders, are based on ameliorating behavioral symptoms, not reversing drug- and stress-induced synaptic pathology that has the potential to cure disorders. This failing arises in part from a research focus limited to understanding how pre and postsynaptic physiology is changed when in fact key neuropathology exists in the perisynaptic neuropil that homeostatically regulates synaptic transmission. I will review recent preclinical findings from our lab and others using animal models of substance use and stress disorder that point to a key role by perisynaptic astroglia and signaling in the extracellular matrix (ECM) in regulating stress- and drug-induced synaptic pathology. These data reveal that drug and stress insults initiate long-lasting changes in brain synapses via enduring neuroadaptations in astroglia and the ECM. Moreover, conditioned cue-induced drug seeking and stress responses arise from transient post-synaptic plasticity that is orchestrated by equally transient morphological changes in perisynaptic astroglia and ECM signaling. I will conclude the presentation with a discussion on how to further understand and therapeutically employ extrasynaptic regulators in treating substance use and stress disorders.

What is "optimal" brain development? It depends on a child's environment

Silvia Bunge
Department of Psychology & Helen Wills Neuroscience Institute,
University of California Berkeley

There has been an explosion of research on human brain development over the past 20 years. As a result, we have learned a lot about the features of brain anatomy and brain function that change over childhood and

adolescence and that help to explain individual differences in cognition, affect, and behavior. However, the vast majority of brain imaging study samples skew towards middle- or higher-income individuals; we know next to nothing about how the brain develops in children living in poverty. Here, I describe a pattern of brain communication that has been shown in a number of studies to be associated with better cognitive performance – and then show how this finding does not generalize to children living below the poverty line. This work serves as a reminder that biological features that are adaptive for one population may not be for another.

An in vitro model to study the early pathophysiology of amyotrophic lateral sclerosis

Andrea Nistri
Dept Neuroscience, SISSA, Trieste, Italy

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease affecting motoneurons with ensuing paralysis and fatal outcome. There is currently no cure for this condition which belongs to the class of diseases caused by intracellular protein misfolding whose origin remains obscure. Elucidating this process remains difficult because ALS is often diagnosed with delay, thus preventing recognition and ideally treatment of the disease at its earliest stage. One important cause of motoneuron distress that might trigger a cascade of cellular events leading to late neurodegeneration is excessive buildup of extracellular glutamate, the main excitatory neurotransmitter at the level of motoneurons. These cells would therefore become overexcited and suffer from “excitotoxicity” with subsequent neuronal death. Our lab has developed a new model of motoneuron excitotoxicity by pharmacological block of the glutamate clearance system in the rat brainstem and observed with patch clamping and calcium imaging the gradual onset of group bursting whereby motoneuron clusters (recruited via gap junctions) generate strong rhythmic discharges that slowly evolve to neuronal death. We have shown that pharmacological approaches to depress excitation by enhancing inhibition or blocking excitatory currents prevent the generation of this deadly rhythmic activity and rescue motoneurons from degeneration, suggesting a potential early target to combat the development of ALS.

Of Synapses and Domesticated Viruses

Vivian Budnik
University of Massachusetts Chan Medical School

The functional role of “junk DNA” in the organism, and in particular the nervous system, is largely unknown. However, new evidence suggests that a master regulator of synaptic plasticity, activity-regulated cytoskeleton-associated protein (Arc) is a domesticated transposable element (TE) that serves as a mechanism to transport RNAs across the synapse. In this mechanism, the ViSyToR (Viral Synaptic Transfer of RNA) pathway, Arc protein forms viral-like capsids that package arc RNA. These capsids are loaded into extracellular vesicles that travel across synaptic partners to provide a signal for new synapse formation. New unpublished evidence suggests that another TE, Copia, thought to belong to the junk DNA has a physiological function at synapses that antagonizes the action of Arc. These studies lend further support to recent arguments and data suggesting that TEs and potentially other types of junk DNA are not junk after all.

Lipid dynamics in synaptic plasticity: lessons from Niemann Pick diseases

María Dolores Ledesma
Centro Biología Molecular Severo Ochoa, CSIC-UAM Madrid, Spain

Dynamic changes in the structure and composition of the membrane protrusions forming dendritic spines underlie the synaptic plasticity required for memory, learning and emotional processes. Efforts have been made to characterize the protein machinery controlling spine dynamics but we know much less about the involvement of lipids despite being major membrane components. Sphingomyelin and cholesterol are

particularly enriched in synapses. Imbalance in the levels of these lipids lead to cognitive and psychiatric alterations as in Niemann Pick diseases. In the talk I will present evidence obtained in mouse models for these disorders supporting a relevant role for sphingomyelin and cholesterol in synaptic plasticity by influencing actin dynamics, calcium homeostasis and neurotransmitter receptor physiology. We will also present data on how these lipids are regulated at spines, on the pathological consequences of their alterations and on strategies to counteract these consequences that open therapeutic perspectives for the currently fatal Niemann Pick diseases.

Striatins in peripheral nerve development

M. Laura Feltri
SUNY at Buffalo

During development, Schwann cells undergo extensive cytoskeletal reorganization as they insert cytoplasmic extensions into axon bundles to sort, ensheath, and myelinate axons. This process is regulated by Rac1. Our lab previously demonstrated that Rac1 activation during development is driven by engagement of alpha6beta1 integrin with laminins, and that this is essential for radial sorting. Additionally, we showed that the co-transcriptional activatosr YAP and TAZ, downstream of the Hippo pathway, are also essential for Schwann cell development and control alpha6beta1 integrin expression. Here we performed a proteomic screen to identify novel Rac1 effectors in peripheral nerves and identified striatin-3 (Strn3) as a candidate. In vitro and in vivo data indicate that striatins are essential for Schwann cell development and myelination, probably by connecting Rac1 to the inhibition of the Hippo pathway.

"Ranwell Caputto" Lecture:

Steady changes in the composition of the neuronal plasma membrane are an early event of the brain aging phenotype

Carlos Dotti
Centro de Biología Molecular Severo Ochoa (CSIC/UAM),
Universidad Autónoma de Madrid, Spain

Aging comes with a panoply of changes in genomic and non-genomic activities (i.e. mitochondrial dysfunction, altered intracellular trafficking, proteostasis defects, calcium dyshomeostasis, etc.). Is there a “master” mechanism upstream of all (or some) of these defects? A change that satisfies this condition is hormonal signalling: it is altered with age, it occurs in all cells of our organs and tissues, and influences genomic and non-genomic activities. Hormonal systems that change with age and contribute to the functional decline typical of old age are the thyroid hormone system, sex hormones, the growth hormone superfamily, and the insulin-like growth factor (IGF) superfamily. In addition to these hormones, glucocorticoids, mainly cortisol must also be considered. While some of the defects in hormone signalling with age may be due to an intrinsic mechanism of age (sex hormones), in others the defect is not in hormone levels but in their ability to induce an effect upon binding to their cognate receptors. This type of defect is known as hormone signal resistance. Therefore, the question to ask now is what is hormone resistance with age (in the central nervous system we must add resistance to neurotransmitter signalling) due to?. In my talk I will present data that suggest that small but persistent changes in the lipid composition of the plasma membrane with age cause the loss of signaling power of (different) membrane receptors, and how these changes occur.

SYMPOSIA

SYMPOSIA

Asymmetries in the human brain: Insights from structural and functional anatomy, and its relation to behavior

Chair: Lucia Alba-Ferrara / ENyS - CONICET

Brain asymmetry has been observed in vertebrates and invertebrates structurally, functionally, and behaviorally, and can arise through several genetic, epigenetic, or neural mechanisms. It is considered an evolutionary advantage: a functionally asymmetric brain prevents conflicts between both hemispheres, performs a parallel processing of tasks, and avoids duplication of functions, increasing neural capacity. The more lateralized a function, the better it works, although extreme lateralizations are not good: the necessary degree of lateralization depends on the task. This symposium will address structural asymmetries in the human brain, and it will focus on regions involved in language processing, a strongly lateralized cognitive domain. Then, evidence from a behavioral paradigm which measures language lateralization will be presented. This original paradigm has the advantage of being transcultural, and its robust results have been replicated in speakers of different tongues. Finally, the clinical use of this paradigm as a presurgical brain mapping tool measuring language lateralization will be discussed.

Anatomical substrates of functional hemisphere asymmetries

MARIANA BENDERSKY
Universidad de Buenos Aires- ENyS

Brain asymmetry has been observed in vertebrates and invertebrates structurally, functionally, and behaviorally, and can arise through several genetic, epigenetic, or neural mechanisms. It is considered an evolutionary advantage: a functionally asymmetric brain prevents conflicts between both hemispheres, performs a parallel processing of tasks, and avoids duplication of functions, increasing neural capacity. The more lateralized a function, the better it works, although extreme lateralizations are not good: the necessary degree of lateralization depends on the task. This symposium will address structural asymmetries in the human brain, and it will focus on regions involved in language processing, a strongly lateralized cognitive domain. Then, evidence from a behavioral paradigm which measures language lateralization will be presented. This original paradigm has the advantage of being transcultural, and its robust results have been replicated in speakers of different tongues. Finally, the clinical use of this paradigm as a presurgical brain mapping tool measuring language lateralization will be discussed.

The translingual lexical decision task: a measure of language lateralization

MARKUS HAUSMANN
University of Durham, UK

The visual half-field technique is a reliable neuropsychological measurement of language lateralization, typically showing higher accuracy and faster correct responses for linguistic stimuli presented in the right visual field (RVF) than left visual field (LVF). The RVF advantage corresponds to the well-known dominance of the left hemisphere (LH) in processing language(s). However, neuroscientists around the globe use different variations of the visual half-field paradigm, preventing direct comparisons. The current study used a word/non-word visual half- field paradigm with translingual stimuli. In total, 496 participants from seven European countries were assessed: Belgium (64), England (49), Germany (85), Italy (34), The Netherlands (87), Norway (51), and Switzerland (126). All language groups revealed a significant RVF/LH advantage in accuracy and reaction times that accounted for up to 26.1% of the total variance in performance. We found some variation in the degree of the RVF/LH advantage across language groups, accounting for a maximum of 3.7% of the total variance in

performance. The RVF/LH advantage did not differ between subsamples speaking English, French or German as first or second languages or between monolingual and early/ late bi/multilinguals. The translingual lexical decision task (TLDT) is a simple but reliable measurement of language lateralization that can be applied clinically and experimentally across linguistic and national boundaries.

Lateralization of lexical processing in refractory temporal epilepsy

LUCIA ALBA-FERRARA
ENyS - CONICET

In temporal lobe epilepsy (TLE) language areas could be functionally affected. This research studied the lateralization of lexical processing in refractory TLE in a non-invasive manner that overcomes the idiom barrier. This paradigm called Lexical Decision Task (LDT) applies the half visual field technique. Patients with left TLE (LTLE) (N=12), right TLE (RTLE) (N=15) and controls (N=17) were evaluated using LDT. An ANCOVA analysis was performed, with the left, right and baseline stimulus side (SS) as a within subjects, and group as a between subject´s variable. A main effect of the SS was found. Pairwise comparisons show that baseline improved performance, right SS resulted in an intermediate performance and the left SS diminished performance. A main group effect was found ($F(2.71)=10, P<0.05$). Comparisons in pairs indicate that the controls outperformed both TLE groups. LTLE and RTLE did not differ from each other. An interaction between group and SS was found. Post hoc t tests showed between the SS of each group showed that controls benefit with right SS compared to left. Such advantage was not found in the LTLE group. The results validate a lateralization of the lexical processing, indicating the effectiveness of the LDT. The interaction between SS and LTLE might indicate diminished lateralization of lexical processing in LTLE, being understood as a sign of a reorganization of the lexical function by epileptogenic crises. Further data is being collected.

SYMPOSIA

Cytoskeleton, its alterations, and neuronal defects

Chair: Gaston Bisig / CIQUIBIC-DQBRC. Fac. Cs Químicas. UNCba

New discoveries in cytoskeletons components and interactions, implication of tubulin c-terminus in neuronal alterations relevant in neuropathologies.

Tau, a key molecule in neurodegeneration from cytoskeleton to microtubule-non related functions.

ALEJANDRA ALONSO
City University of New York, CSI

Tau, a neuronal microtubule associated protein, plays a key role in cognitive processes. Deposits of abnormal forms of tau are associated with several neurodegenerative diseases, including Alzheimer disease (AD), the most prevalent, and Chronic Traumatic Encephalopathy (CTE), the most recently associated to abnormal tau. Tau post-translational modifications (PTMs) are responsible for its gain of toxic function. We were the first to show that the pathological tau isolated from AD brains has prion-like properties and can transfer its toxic function to the normal molecule. Furthermore, we reported that the pathological changes are associated with tau phosphorylation at Ser199 and 262 and Thr212 and 231. We have generated a transgenic mouse model that expresses pathological human tau (PH-Tau) in neurons at two different concentrations (4% and 14% of the total endogenous tau). Expression of PH-Tau causes cognitive decline by at least two different mechanisms: one that involves the cytoskeleton with axonal disruption (at high concentration), and another in which the apparent neuronal morphology is not grossly affected, but the synaptic terminals are altered (at lower concentration). We have evidence that tau interacts with proteins involved in the in the processing of mRNA, suggesting that the changes in tau might be involved in changes of proteostasis. Understanding tau's biological activity on and off the microtubules will help shed light to the mechanism of neurodegeneration.

Implication of α-tubulin tyrosination/detyrosination cycle In synaptic activity and degeneration

LETICIA PERIS
U. Grenoble

Microtubules (MTs) are essential for neuronal morphogenesis and synaptic activity. While dynamic MTs are mainly composed of tyrosinated tubulin, long-lived MTs contain detyrosinated tubulin, suggesting that the tubulin tyrosination/detyrosination (Tyr/deTyr) cycle is a key player in the maintenance of MT dynamics and neuronal homeostasis, conditions which go awry in neurodegeneration. In the Tyr/deTyr cycle, the C-terminal tyrosine of α-tubulin is removed by tubulin carboxypeptidase complex composed of Vasohibin (VASH 1 and 2) and Small Vasohibin Binding Protein (SVBP) and re-added by tubulin-tyrosine-ligase (TTL). Reduced TTL expression induced a decreased tyrosinated dynamic MTs, reduced dendritic spine density, and defective synaptic plasticity and memory. TTL reduction and modified tubulin accumulation is also a feature of Alzheimer's disease (AD), a neurodegenerative disorder characterized by progressive memory loss, amyloid accumulation and cognitive impairment. At neuronal level, the synapses visited by dynamic MTs are more resistant to amyloid toxicity and that expression of TTL, by restoring MT entry into spines, suppresses synapse loss induced by amyloid exposure. Our results demonstrate that a balanced Tyr/deTyr cycle is necessary for the maintenance of synaptic plasticity, is protective against amyloid-induced synaptic damage, and that this balance is lost in AD, providing evidence that defective tubulin re-tyrosination may contribute to circuit dysfunction in AD

In situ organization of the actin/spectrin membrane-associated periodic skeleton of axons with nanometer resolution

NICOLÁS UNSAIN
Laboratorio de Neurobiología, Instituto de Investigación Médica Mercedes y Martín Ferreyra, INIMEC-CONICET, Universidad Nacional de Córdoba (UNC)

Recently, actin, spectrin and associated proteins have been discovered to form a membrane-associated periodic skeleton (MPS) that is ubiquitously present in mature axons of all neuronal types evaluated up to the moment. MPS is a periodic protein structure consisting of actin "rings" located transversely to the axon and separated every 190 nm by α / β-spectrin "spacers" extended along the axon. Since its discovery, the characterization of MPS has been performed almost exclusively in cultured neurons; namely artificial environments in two dimensions. Hence, we proposed to study the spatial organization and biology of these structures in their "natural" environment, that is, in situ. Moreover, it is still not clear how spectrin tetramers are organized in each segment of this periodic scaffold. Taking all this into account, we have begun to analyze the transversal organization of spectrin tetramers in the MPS of axons within mouse nerves, namely optic and sciatic nerves. The MPS cannot be evidenced by conventional fluorescence microscopy, since its periodicity (~190 nm) is below the resolution limit (~250nm). To reach the needed resolution in tissue, we are combining 3D-STOchastic Reconstruction Microscopy (STORM) and tissue Expansion Microscopy (ExM) to gain both resolution and transparency. I am going to present data that allow us to identify common and distinct organization rules of the spectrin tetramers within the MPS in nerve tissue.

α-tubulin c-terminal modification: the importance of being tyrosinated.

GASTON BISIG
CIQUIBIC-DQBRC. Fac. Cs Químicas. UNCba

The C-terminal tyrosine (Tyr) of the α-tubulin chain is subjected to post-translational removal and readdition in a process termed the "detyrosination/tyrosination cycle". L-Dopa and L-Phenylalanine (Phe) can be incorporated into tubulin in place of tyrosine. We described that the presence of L-Dopa in tubulin affects microtubules dynamics, mitochondrial traffic, and KIF5B affinity for Dopa-tubulin-containing microtubules. These findings could be relevant for the neuronal defects observed in Parkinson's disease patients treated with L-dopa for long periods of time. When Phe was the analogue incorporated into tubulin, we observed that not only microtubules dynamics and mitochondrial traffic were altered, but in this case neurites retraction and cell proliferation were also affected. Since it is known that Phe is increased in phenylketonuria, it is conceivable the possibility that Phe incorporation into tubulin is the first event (or among the initial events) in the molecular pathways leading to brain dysfunctions that characterize this neurological disorder. We found that, even though the analogues of Tyr incorporated into tubulin are different, they similarly affect neuronal microtubules functions, and this raises the question whether these alterations are caused by the analogue presence by itself or by disbalancing the detyrosinated/tyrosinated tubulin content.

SYMPOSIA

Neuroscience and Translational Pain Research

Chairs: María Florencia Coronel / Laboratorio de Dolor en Cáncer, Instituto de Investigaciones en Medicina Traslacional CONICET - Universidad Austral. José Biurrun Manresa / Institute for Research and Development in Bioengineering and Bioinformatics, IBB-CONICET-UNER

The symposium will present recent advances in modern neuroscience, ranging from studies in animal models to human clinical trials, in relation to research of the most common, debilitating, and often undertreated condition affecting human health: pain. In the first lecture, Dr. Eduardo Souza-Silva will review the neurobiology of musculoskeletal nociception and the sensory role of histamine, a biogenic vasodilator amine involved in biochemical processes of the immune response. Also, the evidence found so far to validate the existence of a potential analgesic mechanism involving peripheral activation in the knee joint will be presented. The second presentation by Dr. José Biurrun Manresa, will be centered onhuman surrogate models of nociception and pain, describing how the knowledge from animal experiments is translated into human research, focusing on the development and assessment of models for central sensitization. Afterwards, Dr. Margarita Calvo, will present recent clinical findings demonstrating that chronic cutaneous injury can lead to injury and dysfunction of the most distal part of small sensory fibres in a length-dependent distribution resulting in disabling neuropathic pain. Finally, Dr. Pablo Brumovsky will review the antiallodynic and anti-inflammatory effects of IMT504, an oligodeoxynucleotide with immunomodulatory , in various animal pain models, as well as in a phase I-II clinical trials.

Antinociceptive effect of intra-articular histamine in rats

EDUARDO SOUZA SILVA

Universidade Federal de Santa Catarina

Histamine is a biological amine that acts on 4 types of receptors (H1-H4). The sensory role of histamine has been attributed mainly to its actions on H1R in cutaneous tissue, being accepted as a mediator of hyperalgesia in inflammation. Evidence supporting the nociceptive role for histamine in skin tissue in some cases may have been overestimated due to the low selectivity of H1 antihistamines, histamine concentrations above what can be released per gram of skin tissue, histamine activity in tissue cells or even the ambiguity of the sensations of itching and pain in the skin tissue. Although it is found in synovial fluid in different conditions of arthritis, the role of histamine in inflammatory pain is poorly understood. Our results show that H1 antihistamines promote hyperalgesia and, conversely, histamine reduces inflammatory joint pain. We highlight strong evidence for the role of the spinal cord in the hyponociceptive action of joint histamine suggesting the possibility of a mechanism that could help the development of new pharmacological strategies for the treatment of clinically relevant pain that usually originates from joint structures.

Human surrogate models of pain

JOSÉ BIURRUN MANRESA

Institute for Research and Development in Bioengineering and Bioinformatics, IBB-CONICET-UNER

Clinical trials in pain patients are usually a costly and time-consuming process, and they always involve a degree of heterogeneity with regards to the factors that could potentially interact with the neurophysiological mechanisms under evaluation. Prior evaluation of the efficacy of new drugs or alternative methods for pain relief in surrogate models serve as an initial proof of concept and help improving study designs and defining relevant efficacy parameters in subsequent clinical trials. While animal models are useful to get a better understanding of the neurobiology and mechanisms involved in nociception, these findings often do not translate to patients with chronic pain conditions. Hence, surrogate models of nociception and pain in healthy volunteers are necessary to translate data from animals to humans. This talk will present a description of the most common human surrogate models, describing how the knowledge from animal experiments is translated into human research, with particular focus on the development and assessment of models for central sensitization.

Small fibre neuropathy secondary to skin damage

MARGARITA CALVO
Pontificia Universidad Católica de Chile

Small fibre neuropathy (SFN) is a disease that affects exclusively the un myelinated or thinly myelinated sensory and autonomic fibres. The main symptom are pain, itch and dysautonomy. It complicates several common diseases, such as diabetes mellitus and HIV, and the associated pain contributes significantly to the morbidity of these diseases. SFN is the most common polyneuropathy with an estimated incidence of 11.7 cases/100,000/y. The neurobiology of SFN is not well understood, hindering the development of new treatments. SFN is diagnosed based on presence of symptoms (pain or itch), plus abnormal thermal sensation, and a reduction in the density of small fibers in the epidermis. Small fibers innervate the epidermis and convey thermosensation, nociception and itch from the skin through sensory peripheral nerves to the dorsal horn. SFN is believed to occur due to a specific type of axonal degeneration called “dying back”. Neurons with their axons degenerating become hyperexcitable as a consequence of altered gene expression and post-translational modification of voltage gated sodium and potassium channels, leading to severe pain or itch or both. The causes of SFN are only found in around 50% of patients at initial workout. In here we will show that a potentially important and frequently overlooked cause of SFN are chronic inflammatory skin conditions such as Recessive Dystrophic Epidermolysis Bullosa and Lichen simplex chronicus.

IMT504 and chronic pain: A “bench to bedside” tale

PABLO BRUMOVSKY
Instituto de Investigaciones en Medicina Traslacional

Chronic pain, caused either by inflammation or peripheral neuropathies, affects millions of patients around the World. Many of these patients remain undertreated, as most drugs currently available to control pain have limited efficacy and/or exert serious adverse effects. In recent times, the role of the immune system in the mechanisms of pain is receiving serious attention, also for the development of new therapeutic agents. IMT504 is an oligodeoxynucleotide (ODN) with immunomodulatory and tissue repair properties. Work in our laboratory for the past 15 years has exposed remarkable antiallodynic and anti-inflammatory effects in various animal pain models. In the present talk, we will review these effects and relate them to recent findings on the role of different types of immune cells and mesenchymal stem cells. This will be followed by an elaboration on the steps taken thus far in relation to the validation of IMT504 as a therapeutic agent for the treatment of inflammatory or neuropathic pain in humans, through the development of a phase I-II clinical trial.

SYMPOSIA

In vivo selective manipulation of microglia

Chair: Lorena Rela / IFIBIO Houssay, Universidad de Buenos Aires Facultad de Medicina y CONICET

Microglial cell physiology has become a topic of interest, because they have been identified as key modulators of neuroinflammation and nervous system plasticity. In order to disentangle their roles it is crucial to manipulate microglial cells in vivo using selective tools.This symposium will cover the applications of a variety of genetic and pharmacological tools that have become available in in the recent years to interfere with microglia functions in animal models of healthy and diseased nervous systems.

The use of CSF1R inhibitors to manipulate microglia in the healthy and diseased brain.

KIM GREEN

Department of Neurobiology and Behavior, University of California, Irvine, USA

Microglia, the brain's immune sentinels, have garnered much attention in recent years as their roles in maintaining brain homeostasis and as critical enactors of brain disease and injury have come to light. We previously discovered that microglia were dependent on signaling through the colony-stimulating factor 1 receptor (CSF1R) for their survival and developed CSF1R inhibitor paradigms that allow for the rapid and sustained elimination of the microglial tissue from the CNS. The varying degrees of spatiotemporal manipulation afforded by this pharmacological approach allows for microglial ablation prior to, during, and/or following insult, injury or disease. Here, we will show the various ways that CSF1R inhibitors can be employed to manipulate microglia in vivo – from extended depletion to elucidate their functions in the healthy and diseased brains, to repopulation of a replacement tissue from a variety of myeloid cell sources, and in normalization of dyshomeostatic microglia in disease.

Neurovascular Interactions: Unlocking drivers of neurodegeneration

KATERINA AKASSOGLOU

Gladstone Institutes and University of California, San Francisco (UCSF), USA

The communication between the brain, immune and vascular systems is a key contributor to the onset and progression of neurological diseases. We discovered the coagulation factor fibrinogen as a blood-derived driver for neuroinflammation in a wide range of neurologic diseases, such as multiple sclerosis, Alzheimer's disease and brain trauma 1 . We showed that fibrinogen is necessary and sufficient for neurodegeneration and a new culprit for microglia-mediated oxidative stress-dependent spine elimination and cognitive impairment 2 . Microglial surveillance is a key feature of brain physiology and disease. We showed that G i -dependent microglial dynamics prevent neuronal network hyperexcitability 3 . By generating Mg-PTX mice to genetically inhibit G i in microglia, we showed that sustained reduction of microglia brain surveillance and directed process motility induced spontaneous seizures and increased hypersynchrony after physiologically evoked neuronal activity in awake adult mice, suggesting that G i -dependent microglia dynamics may prevent hyperexcitability in neurological diseases. By developing Tox-Seq, we reported the oxidative stress innate immune cell atlas in neuroinflammation. We discovered a first-in-class fibrin-targeting immunotherapy to selectively target inflammatory functions of fibrin without interference with clotting with potent therapeutic effects in autoimmune- and amyloid-driven neurotoxicity 4 . These findings could be a common thread

Microglial activation influences the affective state.

DAVID ENGBLOM

Department of Biomedical and Clinical Sciences (BKV), Center for Social and Affective Neuroscience (CSAN), Linköpking University, Sweden

Many diseases are inflammatory or have an inflammatory component. In these diseases, patients often experience a feeling of sickness that severely reduce their quality of life. Several lines of evidence indicate that inflammatory signaling is a key driver of the depressive mood associated with “classic” inflammatory diseases but also contribute to emotional and cognitive symptoms in neurodegenerative and psychiatric diseases including major depression. The molecular and cellular nature of the “inflammatory signaling” that is critical for the symptoms are in most cases not known but microglia are obvious candidates. To investigate how microglial activation influences affective functions, we have used a model in which we activate microglia in a highly selective way with genetic techniques in mice. Using injection of viral vectors in combination with Cre/loxP methodology, we expressed activating DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) selectively in microglial cells in the striatum. Activation of these receptors with the designer drug CNO induced a negative affective state. Furthermore, inhibition of microglial activation using inhibitory DREADDs (or microglia-specific intervention with IL-6 or prostaglandin synthesis) blocked inflammation-induced aversion. Collectively, these findings show that microglial activation induces a negative affective state and that DREADDs are efficient tools for the study of microglia function.

Effect of microglial depletion on neurodegeneration in a multiple sclerosis model

LAURA ANDREA PASQUINI

Universidad de Buenos Aires. Facultad de Farmacia y Bioquímica. Departamento de Química Biológica. Cátedra de Química Biológica Patológica. Buenos Aires, Argentina. 2. Universidad de Buenos Aires-CONICET. Instituto de Química y Fisicoquímica Biológicas (IQUIFIB). Buenos Aires, Argentina

Multiple sclerosis (MS), especially in its progressive pattern, involves early axonal damage resulting from demyelination and loss of trophic support, in association with astrocyte- and microglia-mediated inflammation in the central nervous system (CNS). Prolonged cuprizone (CPZ) intoxication is widely used as a MS model, as it triggers chronic demyelination, neurodegeneration, astrogliosis and microgliosis. While reactive MG can damage tissue, exacerbate deleterious effects and contribute to neurodegeneration, their role in myelin debris phagocytosis during demyelination proves crucial in enabling oligodendroglial differentiation and bringing about remyelination. As MG are physiologically dependent on colony-stimulating factor 1 receptor (CSF-1R) signaling, MG can be almost completely eliminated from the brain using CSF-1R inhibitors. Therefore, we aimed to evaluate the effects of CSF-1R inhibitor BLZ945 on myelin status, neurodegeneration and astrogliosis during chronic CPZ demyelination. Mice were fed either control or CPZ chow for 12 weeks and orally gavaged vehicle or BLZ945 as from the 2nd week of CPZ treatment. BLZ945 induced a reduction in the microglial population in all structures evaluated. Moreover, the recovery in myelin basic protein (MBP) and myelin lipids showed BLZ945 to protect myelin. However, no significant correlation was found between myelin and axonal protection, as axonal degeneration was more prominent upon BLZ945 treatment along with astroglial activ

SYMPOSIA

How does the brain represent what we know (and don't know) about the world?

Chairs: Rodrigo Echeveste / sinc(i), CONICET-UNL. Ines Samengo / Department of Medical Physics, Centro Atómico Bariloche and Instituto Balseiro

The computations involved in perception, reflections about the world, and action planning, are not performed on external stimuli, but rather on our internal representations of those stimuli. Therefore, the aspects of reality our sensory systems happen to represent, and the specific way in which those representations are instantiated in a neural code, fundamentally constrain the way we experience and interpret the world. Moreover, several neuropsychiatric disorders are presently postulated to result from an anomalous representational structure. This symposium summons four neuroscientists with computational background to discuss the structure of representations of different aspects of the physical world, such as our location in space, the orientation and color of visual stimuli, and the temporal structure of vocal productions. Specific emphasis is made on the geometric structure that the neural code imparts on the represented space, on the encoding of the degree of uncertainty about the represented stimulus, and on the relevance of the temporal structure of the code. The purpose is to employ computational tools to characterize the biases, capacities and limitations of the so-called "eye of the beholder" as a first step in our understanding of both typical and atypical phenomenal experience.

Neural coding of sound envelope structure in songbirds

ANA AMADOR

Dept. of Physics, University of Buenos Aires and IFIBA, CONICET, ARGENTINA

Songbirds are a well-established animal model to study the neural basis of learning, perception and production of complex vocalizations. In this system, telencephalic units in the neural nucleus HVC present a state-dependent, highly selective response to auditory presentations of the bird's own song (BOS). This property provides an opportunity to study the neural code behind a complex behavior. Here, I will show that subtle changes in the temporal structure of the sound envelope of the song can drive changes in the neural responses of highly selective HVC units. In this work, we generated an envelope-modified BOS (MOD) by reversing each syllable's envelope but leaving the overall temporal structure of syllable spectra unchanged, which resulted in a subtle modification for each song syllable. We conducted in vivo electrophysiological recordings of HVC neurons in anaesthetized zebra finches (Taeniopygia guttata). Units analyzed presented a high BOS selectivity and lower response to MOD, but preserved the profile response shape. These results show that the temporal evolution of the sound envelope has a specific neural representation in the avian song system.

A bridge between physiological and perceptual views of autism by means of sampling-based Bayesian inference

RODRIGO ECHEVESTE

sinc(i), CONICET-UNL

Theories for autism spectrum disorder (ASD) have been formulated at different levels: ranging from physiological observations to perceptual and behavioural descriptions. Understanding the physiological underpinnings of perceptual traits in ASD remains a significant challenge in the field. Here we studied the link between Bayesian computations under weakened priors, and inhibitory dysfunctions, neural variability, and oscillations in ASD subjects. We worked with a recurrent neural-network (RNN) model which had been trained to perform inference in a visual task via sampling. We took two parallel paths: In one of them, we modified the probabilistic generative model under which the stimuli are assumed to be generated in order to increase the uncertainty of the prior distribution. In the other, we weakened the inhibitory connections in the neural network to induce an inhibitory dysfunction. We found that both paths lead to consistent results in terms of the represented posterior distributions, providing support for the view that both descriptions might constitute two sides of the same coin. Furthermore, the dynamical properties of the network performing Bayesian inference allowed us to make connections between probabilistic computations and previous observations in terms of neural variability, oscillations and transient responses in the ASD population.

The geometry of color space

INES SAMENGO
Department of Medical Physics, Centro Atómico Bariloche and Instituto Balseiro

Our sensory systems transform external signals into neural activity, from which percepts are produced. We are endowed with an intuitive notion of similarity between percepts, that need not reflect the proximity of the physical properties of the corresponding external stimuli. The quantitative characterization of the geometry of percepts is therefore an endeavour that must be accomplished behaviorally. Here we characterized the geometry of color space using discrimination experiments. We proposed an individually tailored metric defined in terms of the minimal chromatic difference required for each observer to differentiate a stimulus from its surround. Additional discrimination and matching experiments demonstrated that the metric derived from the first experiment revealed perceptual chromatic effects to be remarkably homogeneous and isotropic throughout color space. We conclude that adequately capturing the geometry of color space reveals the natural symmetries of the computations involved in phenomenology of color perception.

Network architecture shapes spatial representations in the medial entorhinal cortex ...Or does it?

EMILIO KROPFF
Leloir Institute - IIBBA

Entorhinal grid cells have a population activity with striking hexagonal spatial periodicity, a torus in topological terms. This is considered to be possible only as a consequence of the architecture of connections being itself a torus, constraining through attractor dynamics the possible activity states of the network. In more general terms, the word 'dimensionality' referring to an attractor network is used indistinctly to speak about the architecture of connections and the space of representations. Here we present for the first time evidence showing that the architecture of an attractor network and the space of representations can be two distinct topological objects. In a model of grid map formation resulting from self-organized Hebbian learning, we assessed the consequence of adding an architecture of recurrent connections representing a torus (2D) or a ring (1D). We found that both networks have the ability to align all maps to a common set of hexagonal axes, so that population activity is constrained to a torus. The ring architecture, however, is more flexible, generating a family of solutions, which is appealing since grid cells are capable of coding for 1D variables (e.g. time). Our work shows for the first time that the architecture of the grid cell network could be something other than an ad hoc 2D object. It also provides a counterexample against the prevailing intuition that the architecture of a network and the space of representations must go hand in hand.

SYMPOSIA

Bridging the epigenetic landscape with axonal dynamics: transcriptional and translational concepts for development and repair.

Chairs Carlos Wilson / CONICET - Instituto Universitario de Ciencias Biomédicas de Córdoba. Ana Lis Moyano / Centro de Investigación en Medicina Traslacional "Severo Amuchástegui" (CIMETSA) Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC)

Axonal growth is a highly dynamic phenomenon, supported by morphological and biochemical transformations throughout the life of neurons. It starts early in newborn neurons, defining the axon-dendritic compartments, and determines the neurotransmission capacity of the mature neuron. Briefly, growing axons requires specification, extension, pathfinding, and maturation. Moreover, further processing, such as myelination, may be needed to improve neurotransmission. Up to date, several mechanisms controlling axonal growth have been reported, mostly affecting cytoskeleton, trafficking, and axon-glia communication. Nevertheless, genetic regulation has remained understudied. Recent evidence suggests that histone post-translational modifications (PTM) and non-coding RNAs (ncRNAs) are novel epigenetic players strongly linked to axonal growth in health and disease. Therefore, this symposium will be focused on their role in axonal specification, guidance and maturation. In addition, we will discuss the influence of PTMs on axonal recovery after lesions, such as spinal cord injury. Finally, we will approach the therapeutic potential of extracellular vesicles released by stem cells carrying miRNAs, and their role on axonal regeneration capacity and myelination of neurons.

Epigenetic regulation of neuronal polarization and axon growth by the histone methyltransferase G9a and the H3K9me2 label

CARLOS WILSON

CONICET - Instituto Universitario de Ciencias Biomédicas de Córdoba

Neurons are polarized cells, exhibiting the somato-dendritic and axonal compartments; domains specialized in receiving and transmitting signals, respectively. This compartmentalization is the result of decoding extrinsic/intrinsic stimuli, impacting on signaling pathways able to shape the neuronal morphology. In this regard, cytoskeleton remodeling is crucial, since both microtubules (MT) and F-actin (FA) represent the driving force of polarization and axonal development. Although polarity mechanisms have been reported, the genetic fundamentals remain underexplored. Recently, we reported that the histone methyltransferase G9a promotes polarization and axonal growth in cultured hippocampal neurons, by repressing the RhoA-ROCK pathway, a negative regulator of neuronal polarization. In addition, the loss of function of G9a in situ impaired cortical migration of embryonic neurons, suggesting failures on polarization and migration in vivo. Moreover, bi-methylation of H3K9 (H3K9me2), highly dependent on G9a in developing neurons, parallels axon formation in early and mature stages. Accordingly, genetic deletion of nuclear H3K9me2 impairs axonal maturation, visualized by abnormal assembly of the axon initial segment (AIS); the intra-axonal domain in which voltage-dependent ion channels are recruited. Overall, our results suggest a link between epigenetic regulation and axonal development in central neurons through a G9a-H3K9me2 –dependent mechanism.

ncRNAs: a non-canonical mode of intracellular transport through organelle hitchhiking

MARIE-LAURE BAUDET

University of Trento

Most cells are polarized with an intracellular milieu that is not homogenous but partitioned. mRNA localization and its corollary, local translation, are key mechanisms to create and sustain polarity by conferring functional autonomy to a variety of subcellular compartments. Recent evidence suggests that not only mRNAs but also various regulatory RNAs, such as miRNAs and circular RNAs, are localized to and enriched within subcellular outposts. The mechanisms of ncRNA

transport to these compartments remain, however, elusive. This is largely due to the lack of adequate tools to study ncRNA trafficking. We developed labeled nucleic-acid-based approaches to track diverse types of endogenous ncRNAs through live imaging. To achieve this, we exploited the specific features of each ncRNA type under study including their unique sequence and secondary structure. We applied these tools to investigate ncRNA trafficking specifically within axons of the highly polarized neurons as a model subcellular compartment. We uncovered that specific ncRNA species employ a unique mode of transport that relies on organelle hitchhiking. Organelles, in turn, deliver ncRNAs to their site of function. Overall, our results reveal critical insight into the molecular mechanisms of ncRNA subcellular localization. They also provide fundamental knowledge of axonal transport, a process derailed in several incurable neurodegenerative disorders, with potential future therapeutic application

Targeting the CBP/p300 acetyltransferase with a small-molecule activator to enhance axon regeneration and functional recovery after spinal cord injury

THOMAS HUTSON

Swiss Federal Institute of Technology (EPFL)

Injured axons fail to regenerate in the adult mammalian central nervous system (CNS) leading to permanent deficits in sensorimotor function. We have shown that increasing the activity of proprioceptive dorsal root ganglion (DRG) neurons using an enriched environment induces a long-lasting increase in their regenerative potential that is dependent on CREB Binding Protein (CBP) mediated histone acetylation. Systemic application of a pharmacological activator (CSP-TTK21) of the acetyletransferase CBP/p300 acutely after a spinal cord injury (SCI) led to a significant increase in the sprouting of sensory and motor fibres as well as a significant improvement in sensorimotor recovery. Our findings demonstrate the importance of the chromatin environment to the regenerative capacity of neurons. Recovery in chronic injury models is challenging yet could offer huge benefits to patients currently afflicted by SCI. By manipulating key histone modifiers that orchestrate broad changes in gene transcription we aim to further enhance neuroplasticity and achieve significant improvements in axonal sprouting and functional recovery.

Stem Cell-Derived Extracellular Vesicles Promote Regeneration During Demyelination ex vivo

ANA LIS

Centro de Investigación en Medicina Traslacional "Severo Amuchástegui" (CIMETSA) Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC)

Extracellular vesicles (EVs) are a heterogeneous group of nanovesicles that shuttle bioactive molecules (e.g. proteins, lipids and RNAs) and modulate biological functions in recipient cells. EVs secreted by stem cells can promote tissue regeneration and function as potential alternatives to stem cell therapy. Furthermore, EVs have fewer side effects and do not present risks associated with cellular transplants such as incomplete differentiation or tumorigenesis. Recent studies have shown that administration of murine neural stem cells' EVs (mNSC-EVs) promote regeneration and restore neurological functions in animal models of CNS disorders. However, the molecular mechanisms responsible for these biological effects in the CNS are unknown and it is unclear whether human NSC-EVs promote myelin regeneration. Results from our laboratory indicate that EVs secreted by human induced pluripotent stem cells (hiPSC-EVs) and human neural stem cells (hNSC-EVs) promote myelin regeneration in an ex vivo model of CNS demyelination. Considering that EVs can transfer functional coding and non-coding RNA between cells, we performed in silico analyses of small non-coding RNA profiling data from hiPSC-EVs and hNSC-EVs. We found that EVs secreted by hiPSC and hNSC are enriched in small RNAs that control oligodendrocyte proliferation and differentiation. These results indicate that hiPSC-EVs and hNSC-EVs promote the regeneration of myelin at least in part through the transfer of small RNAs.

SYMPOSIA

Neurocognitive perspectives on language researchw

Chair: Laura Kaczer / wIFIBYNE (UBA-CONICET)

Language is a distinctively human capacity that requires the involvement of multiple cognitive networks with functionally distinct contributions. Based on neuroimaging techniques, we are now able to study the neural basis for the processing of phonological, semantic, and syntactic information. To be able to grasp this complexity, language research needs the dialogue between different disciplines such as linguistics, psychology, biophysics, computational science, and anthropology, thus representing a highly interdisciplinary area of research. In this symposium, we will bring together researchers with different backgrounds to discuss the mysteries of how the human brain acquires and represents language and speech. In addition, we hope that this symposium could contribute to promote the collaboration between neuroscience and language-related topics in our community.

Neural and cognitive correlates of the speech auditory-motor synchronization

M. FLORENCIA ASSANEO
Instituto de Neurobiología, UNAM

The interaction between perception and production has been widely studied in the field of cognitive neurosciences, with speech being a case of particular interest. In this direction, it has been demonstrated – by more than one research team – that producing speech modulates the activity of brain areas related to speech perception and vice versa – passive listening to speech actives frontal areas responsible of production. Despite the fact that the speech acoustic signal presents temporal regularities – and that these have been demonstrated crucial to achieve intelligibility – the study of the interaction of the rhythms that characterize the systems of production and perception of speech has been relegated. During this talk I will focus precisely on this aspect. First, I will introduce a deceptively simple behavioral test capable of assessing the individuals' degree of auditory-motor synchronization of speech. Secondly, I will show which structural and functional brain features are predicted by the test outcome. And finally, I will examine how a high -or low- level of auditory-motor synchronization affects different cognitive abilities.

Beyond the 0.001%: linguistic diversity, cognitive neuroscience, and the foundations of the language sciences

DAMIAN BLASI
Harvard University

Most research in language involves a handful of the over 6,500 languages spoken and signed in the world today, with Germanic and Romance languages accounting for most of the lucky set. This has biased our language sciences in at least three critical ways. First, we underestimate the nature and the extent of the variation that could exist across languages. Second, we have focused on linguistic phenomena that are especially relevant for the few languages that have been researched in depth – sometimes by sidelining far more cross-linguistically frequent linguistic aspects. And third, we effectively assume that, when investigating human behavior and cognition, the language(s) used by individuals is largely irrelevant. In this presentation I will argue that the time is ripe for a change in the field – and that we should collectively consider involving other languages in our theorizing and in science-making more in general. I will illustrate this by briefly describing some interesting cross-linguistic differences that have emerged in the cognitive neuroscience of language literature in the last few years. Finally, I will discuss how Latin America is particularly well positioned for leading these changes by integrating the (often neglected) native languages and their users.

Beyond the lonely word: Discourse-level approaches to basic and translational neurolinguistics

ADOLFO GARCÍA
Centro de Neurociencias Cognitivas (Universidad de San Andrés), CONICET y Global Brain Health Institute (University of California, San Francisco)

Over the last 40 years, neurolinguistics has honed our understanding of language (dys)functions through studies on diverse stimulus types. Yet, most studies have employed (pseudo)randomized sequences of isolated, decontextualized words or sentences, neglecting more naturalistic manifestations of language. Do key findings in such traditional paradigms generalize onto context-rich materials, such as narrative texts? And can specific neural disorders be detected by analyzing spontaneous speech? In this presentation, I will survey recent findings from discourse-level approaches to basic and translational neurolinguistics. Our team has developed a multi-methodological framework for healthy persons and neurological patients, yielding new evidence to address the two questions mentioned above. First, we have shown that the same neural networks engaged by specific single-item categories (e.g., action-related and socially-laden words) are critically recruited when such stimuli are embedded in context-rich, cohesive, and coherent stories. Second, our machine learning studies suggest that fine-grained acoustic (e.g., articulatory) and textual (e.g., semantic) properties of spontaneous verbal production allow identifying persons with different neurodegenerative disorders and predicting symptom severity. These lines of work pave the way for a naturalistic neurolinguistic agenda, expanding recent neurocognitive models and revealing candidate markers of highly prevalent brain diseases.

The role of intrinsic reward on language learning

ANTONI RODRIGUEZ-FORNELLS
University of Barcelona / ICREA / IDIBELL

During the last decade we have accrued important knowledge regarding the cognitive and neural mechanisms involved in the hard process of learning a new language, being these studies essential to understand how the brain of bilinguals is sculpted. It is still unknown which are the neural processes underlying the human drive to learn a language and what maintains this effortful activity. Recent models proposed that during evolution, emerging language-learning mechanisms might have been glued to phylogenetically older subcortical reward centers, reinforcing human motivation to learn a new language. Supporting this hypothesis, we showed that adult learners exhibited robust functional MRI activation in core reward-pleasure centers (ventral striatum) when successfully learning the meaning of new-words. These results provided the first neural evidences of a strong coupling between neocortical language regions and the subcortical reward system during language learning. Following this research, we observed that successful active language learning (without external feedback) triggered also the activation of midbrain dopaminergic circuits and the hippocampus. We believe this intrinsically motivated-learning mechanism might be crucial for boosting formation of long-term memories, specially in our everyday lives, as we continually acquire new knowledge in the absence of any obvious immediate reward.

SYMPOSIA

Infant-caregiver interactions shape brain development and have lifelong consequences for mental health

Chair: María Eugenia Pallarés
Laboratorio de Programación Perinatal del Neurodesarrollo, IBCN- Facultad de Medicina, UBA

In mammals, caregivers-offspring interactions are an important developmental cue for the environmental quality that prepares offspring for the conditions of life. Also, these interactions can impact on the individual's growth and behavior. In humans, adverse caregivers-offspring bond includes neglect, maltreatment, and exposure to toxic stress by at least one of the caregivers. Those adverse early bonds raise the risk for psychiatric disorders throughout the lifespan of the individual. In animals, biparental care is relatively rare and these interactions are primarily through the mother. Several rodent models have been established to manipulate the quality of mother-infant interactions during early postnatal life. Evidence from these studies helped to gain a better understanding of the mechanisms by which these interactions impact neurobehavioral development in the offspring and induce later-life behavioral consequences. In this Symposium we present novel knowledge driven by four renown leaders in the field that have used different research approaches to study the impact of maternal care on brain and behavior development in rodent offspring. Although the approach of each speaker is interestingly different, al succeed in delineating a specific aspect of how early-life experiences driven by caregivers influences the offspring outcome. Taken together, their studies strengthen the idea that the trajectory of the developing brain is influenced by early-life experiences.

Mothers neglect their young when peripartum adaptations of the CRF system fail

OLIVER BOSCH
University of Regensburg

The peripartum brain undergoes dramatic changes in order for the mother to become fully maternal. This is the result of a concerted balance of "pro-maternal" versus "anti-maternal" neuromodulators, such as the oxytocin and vasopressin systems on one hand versus the corticotropin-releasing factor (CRF) system on the other hand. When these adaptations fail, the outcome can be dramatic, e.g. leading to postpartum mood disorders with all its consequences for mother and offspring. For example, in the biparental prairie voles, a lactating mother that has lost its male partner experiences increased emotionality but shows normal maternal care. However, the offspring miss the paternal investment. Furthermore, in uniparental mouse and rat mothers, increased activity of the CRF system in maternal brain regions like the lateral septum, the bed nucleus of the stria terminalis or the medial preoptic area leads to reduced maternal investment in the young. This might be partly due to the CRF system directly affecting local oxytocin release. In summary, the behavioral effects of increased CRF signaling on the maternal brain are not only brain region- but also receptor subtype-specific. Such findings might help us to advance our understanding of the complex basis of postpartum mood disorders and the implications of the CRF system therein.

Early life stress and the programming of motivated behaviors and cognition

CARLA DALMAZ
Universidade Federal do Rio Grande do Sul

Early life experiences program lifelong responses to stress, as well as behavior in adulthood, including those related to motivation and cognition. In this sense, resilience and vulnerability to psychopathologies have been suggested to be affected by early adversities. Here we discuss some of the effects of early life experiences on eating behavior and on some aspects of cognition using animal models. Furthermore, we consider some neurochemical alterations possibly underlying these observations.

A translational approach to investigate mechanisms underlying intergenerational inheritance of depression

CHRIS MURGATROYD
Manchester Metropolitan University

Stress during early life such as exposure to prenatal and postnatal depression or receiving reduced levels of parental care can produce long-lasting behavioral effects. Such long-term disruptions in stress-related behaviors have been seen in both human and rodent studies in offspring exposed to a variety early-life stressors such as maternal depression. Importantly, offspring exposed to early life stress have increased susceptibility to maternal depression themselves suggesting a mechanism by which stress could be intergenerationally inherited through maternal stress. We have been exploring the possible mechanisms underlying how maternal stress and reduced care is able to increase the risk of developing stress-related behavioral disorders in the offspring. We found a number of generational changes in neuroendocrine and immune factors together with epigenetic and transcriptome changes supporting these as mechanisms in the transmission of maternal stress. We are now using this work to develop targets that are currently being investigating in relevant human studies.

Developmental transitions in brain networks of attachment and fear: Rodent model of human development

REGINA SULLIVAN
Nathan Kline Institute, New York University Langone Medical Center

We have known since the 1950s that the quality of care infants receive from parents has enduring effects on brain circuits controlling emotion and cognition, as well as ubiquitous changes in gene regulation, epigenetics, myriad neurotransmitters/hormone, and brain anatomy throughout the brain. However, mechanisms by which experiences initiate different developmental pathways remain incompletely understood. Here we focus on one variable during mother-infant interactions: how well the mother buffers (attenuates) the offspring's stress response and aberrant infant behavior. Using a rodent animal model, we have begun to question the neurobiology of social buffering within attachment during typical rearing, as well as within trauma associated interactions with the parent (maltreatment). First, within typical attachment, we present data illustrating how mothers' social buffering of pups' stress response can alter the offspring's amygdala and its network to alter learning about trauma. Next, we present data showing how maltreatment by the mother blunts this neural network processing. Finally, we present within nest neurobehavioral data for ecological significance suggesting the mother is engaged in moment-to-moment regulation of pups' cortical and amygdala oscillations, which is also disrupted in pups maltreated by the mother. For all examples, maternal regulation of the offspring's brain decreases as pup approaches independence and is disrupted by adversity (maltreatment).

SYMPOSIA

Attending the unattended: focusing on rare diseases

Chairs: Patricia Setton / Departamento de Química Biológica, FFyB, IQUIFIB, UBA-CONICET. Juan Ferrario / iB3-UBA / CONICET

The expression "rare diseases" describes a group of pathologies with a very low prevalence which brings about reduced incentives and support for fully investigation as well as appropriate managed by health professionals and in some cases lack of successful therapies. Rare diseases encompass a broad spectrum of pathologies which are defined considering their prevalence rather than by common biochemical, clinical and/or pathophysiological characteristics. Although "rare diseases" highlight the low frequency of this pathologies, bibliographical data reports around 6000 "rare diseases" which altogether affect close to 300 million people worldwide. Including in this group of pathologies are rare genetic diseases which affect the nervous system chronically with a progressive degenerative evolution, generally beginning during the newborn period or during childhood. In the present symposium we will focus on these group of pathologies emphasizing basic research performed to develop experimental models for the study of new therapeutic strategies or to shed light to the mechanisms underlying their pathophysiology, trying to pay attention to these unattended pathologies. Finally, an overview of the situation in Argentina will be presented.

Travelling axons, moving eyes

SARAH GUTHRIE
School of Life Sciences, University of Sussex

The ocular motor system controls eye movements consisting of three cranial nerves connected to six extraocular muscles. A precise sequence of axon guidance events is required for the development of the ocular motor system. The signalling protein alpha2-chimaerin (α2-CHN) plays a pivotal role in the formation of the ocular motor system; mutations in CHN1, encoding α2-CHN, cause the human eye movement disorder Duane Retraction Syndrome (DRS). Our research has demonstrated that manipulation of α2-chn signalling in the zebrafish embryo leads to ocular motor axon wiring defects. We have recently shown that several cytoskeletal regulatory proteins – collapsin response mediator protein 2 (CRMP2), (encoded by the gene dpysl2), stathmin1 and stathmin 2 – bind to α2-CHN. dpysl2, stathmin1 and especially stathmin2 are expressed by ocular motor neurons. Manipulation of dpysl2 and of stathmins in zebrafish larvae leads to defects in both the axon wiring of the ocular motor system and the optokinetic reflex, impairing horizontal eye movements. Knockdowns of these molecules in zebrafish larvae caused axon guidance phenotypes that included defasciculation and ectopic branching; in some cases these phenotypes were reminiscent of DRS. chn1 knockdown phenotypes were rescued by overexpression of CRMP2 and STMN1, suggesting that these proteins act in the same signalling pathway. These findings suggest that CRMP2 and stathmins signal downstream of α2-CHN to orchestrate ocular motor axon gu

Neurological manifestations in Fabry disease with a perspective on new therapies?

DERRRALYNN HUGHES
University College London

Fabry disease (FD) (OMIM#301500) is an X-linked lysosomal storage disorder caused by a mutation in the GLA gene which leads to a deficiency of the enzyme alpha-galactosidase A. This impairment causes the accumulation of sphingolipids in cells from different tissues and organs, particularly globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) and causes dysfunction of various organs including the heart and kidney. FD may also affect the central and peripheral nervous system leading to stroke, white matter lesions, pain, and autonomic disturbance. Manifestations are heterogeneous with an early classical form of the disease generally presenting with acroparasthesia, sweating abnormalities and eye changes before progressing to renal dysfunction and cardiomyopathy; and a later onset form generally affecting to a single organ, notably the heart. Disease in males is usually proceeds that in females and is more severe. Stroke occurs sporadically in

classical and later onset patients however features predicating the occurrence of neurological disease are not well understood. Whilst there is evidence of some effect of Fabry-specific therapy on manifestation such as pain, gastrointestinal disturbance and hearing loss data relating to central neurological events is more limited. A number of new therapies are under development and understanding of their potential impact on neurological manifestations is awaited.

CRISPR/Cas9 for the development of cellular models of lisosomal disorders

PAULA ROZENFELD

IIFP (UNLP-CONICET)

Lysosomal disorders are a group of genetic disorders due to defects in the function of proteins, mainly enzymes, of lysosomes, characterized by accumulation of undegraded substrates in those organelles. Pathophysiological mechanisms that are fired from the genetic defect causing loss of organ function is not completely understood. Knowledge of these mechanisms at molecular level would lead to propose coadjuvant therapies directed to specific targets. For this reason, it is necessary to have in vitro or in vivo models of disease. We have developed cellular models of Gaucher disease by the use of gene editing technology of CRISPR/Cas9 directed to GBA1 gene. We have transfected two cell lines. One is the human monocytic cells THP-1 that are the precursors of macrophages, the main affected cell in Gaucher disease. The other is the U87 glioblastoma cell line, for the evaluation of neurological aspects associated to development of Parkinson disease in Gacuher patients.

Rare Diseases in Argentina

ROMINA ARMANDO

Dr. Romina Armando, Geneticist, Rare Diseases Programa, Ministry of Health

Rare Diseases (RD) has become a new concept in public health. They are a heterogeneous group of pathologies with a very low prevalence in the population. Although few people is affected by each disease, all together they affect more than 3 million argentinian people. In Argentina, the National Law 26689 defines them as those entities whose prevalence is less than 1:2000. It is estimated that there are, at present, approximately more than 6000 different RD, most of them chronic, disabling and approximately 80% of genetic etiology. Despite the fact that they are different entities with diverse clinical presentation, the problems they promote both for the health system and for patients and their families are common (diagnostic delay, visit by many specialists, lack of information, etc.). This scenario triggered other countries to seek solutions by implementing a series of public policies with new strategies that allow the creation of processes and structures aimed at improving the life of patients, families and professionals. In Argentina, since 2015 with the creation of a National Program for RD in the Ministry of Health, strategic lines have been developed to simplify access to health care for patients affected with RD.

SYMPOSIA

Glia-driven neurodegeneration and neurorepair in age-related dementias

Chairs: Daniela Durand / INBIOMED Instituto de Investigaciones Biomédicas UBA-CONICET, Facultad de Medicina, Universidad de Buenos Aires. Carla Caruso / INBIOMED Instituto de Investigaciones Biomédicas UBA-CONICET, School of Medicine, University of Buenos Aires

Although brain aging is accompanied by molecular and synaptic changes, dementias develop with particular hallmarks and lead to impairment in routine memory, skills, and knowledge, affecting daily activities and autonomy. Our knowledge on age-related dementias has grown and diverged from specific protein malfunction to multifactorial components, including glial dysfunction and neuroinflammation. However, it is still debated whether glial dysfunction is an initial step in the cascade of neurodegenerative events in these diseases or if glia is just exacerbating damage after triggering neuroinflammatory pathways. A diversity of disease models can help address these issues. This symposium aimed at collecting significant evidence to reconsider the pathophysiology of age-related neurodegenerative diseases with focus on glial alterations. Consequently, glial cells can be presented as target for disease-modifying therapeutics.

Heterogeneity of microglial activation states in Alzheimer Disease

SUMAN JAYADEV
University of Washington

Microglia-mediated neuroinflammation contributes to disease progression in neurodegenerative diseases such as Alzheimer's Disease (AD). Microglia subtypes are complex, with beneficial and harmful phenotypes. Understanding the gene expression networks which define the spectrum of microglia phenotypes is critical to identifying specific targets for neuroinflammation modulating therapies. We studied post-mortem brain tissue from 22 total individuals, 12 of whom had significant AD neuropathic change. Nuclei isolated from prefrontal cortex were sorted for the myeloid marker PU.1 using fluorescence activated nucleus sorting (FANS) and sequenced with the 10X Genomics Chromium platform. Unbiased clustering revealed 10 microglia clusters we could then annotate based on differential gene expression and pathway analysis. We found a diversity in the various "activation" microglia subtypes, a few of which were either over or under-represented by AD nuclei compared to controls. Trajectory analysis can also reveal differential "paths" taken by AD and control nuclei from inactivated to activated. Our efforts contribute to ongoing efforts in more precise microglia phenotyping for the purpose of tailored neuroimmune therapeutics.

Age-related changes on the activation of microglia promotes neuroinflammation and neuron damage

ROMMY VON BERNHARDI
Facultad de Ciencias de la Salud. Universidad San Sebastian

Our glia-dysregulation hypothesis states that AD is caused by impaired microglia (MG) leading to neuronal dysfunction & neurodegeneration. Aged MG show increased inflammation. Compared with 3 m-old mice, scavenger receptor-A (SRA) is reduced in 12 m-old WT mice, as was already observed in young APP/PS1 mice. SRA is involved in β-amyloid (Aβ) uptake and the inflammatory activation of glia, we compared the activation of MG obtained from WT, SRA-/- & APP/PS1/SRA-/- mice, to assess age-dependent activation, cytokines, and MAPK signal. We assessed cytokine levels by ELISA, and the activation of signaling pathways by WB. The neurotoxicity of activated MG conditioned media (CMs) MG was evaluated on hippocampal neurons by TUNEL. Glia from SRA-/- and triple mice had levels of TNFα & IL1β 7-fold higher, and anti-inflammatory cytokines (IL10 & TGFβ) several-fold lower than WT glia. SRA-/- cells showed complex changes in the activation of signaling pathways and the release of cytokines in response to inflammatory stimulation. CMs of basal MG from SRA-/- mice were more neurotoxic than that of WT mice. SRA-/- MG stimulated with LPS were less neurotoxic that WT cells, whereas Aβ and Aβ+LPS-stimulated MG induction of hippocampal neurons apoptosis was similar for all the

genotypes. Our results show that the inflammatory activation results in reduced cytotoxicity in SRA-/- mice, whereas activation by Aβ is preserved. SRA appears to participate in a complex regulation of the activation of MG.

Late neurological consequences of early life infections: the role of microglia

JULIA CLARKE
Federal University of Rio de Janeiro

Harmful environmental stimuli during critical stages of development can profoundly affect behavior and susceptibility to diseases. Alzheimer disease (AD) is the most frequent neurodegenerative disease, and evidence suggest that inflammatory conditions act cumulatively, contributing to disease onset. Here we investigated whether infection early in life can contribute to synapse damage and cognitive impairment induced by amyloid-β oligomers (AβOs), neurotoxins found in AD brains. To this end, wild-type mice were subjected to neonatal (post-natal day 4) infection by Escherichia coli (1 × 104 CFU/g), the main cause of infection in low-birth-weight premature infants in the US. E. coli infection caused a transient inflammatory response in the mouse brain starting shortly after infection. Although infected mice performed normally in behavioral tasks in adulthood, they showed increased susceptibility to synapse damage and memory impairment induced by low doses of AβOs (1 pmol; intracerebroventricular) in the novel object recognition paradigm. Using in vitro and in vivo approaches, we show that microglial cells from E. coli-infected mice undergo exacerbated activation when exposed to low doses of AβOs. In addition, treatment of infected pups with minocycline, an antibiotic that inhibits microglial pro-inflammatory polarization, normalized microglial response to AβOs and restored normal susceptibility of mice to oligomer-induced cognitive impairment. Interestingly, mice infected with b

Modulating glial cells response in the aging brain: use of IGF1 gene therapy as a therapeutic tool

MARIA JOSE BELLINI
Instituto de Investigaciones Bioquímicas de La Plata "Profesor Doctor Rodolfo R. Brenner" (INIBIOLP), CONICET-Facultad de Cs. Médicas-UNLP

Our research focuses on the modulation of neural cells and brain outcomes during aging process employing Insulin-like growth factor-1, which is essential for synaptic plasticity and neuronal survival. We reported some benefits of IGF-1 gene therapy (IGF1-GT). Here we explored the effects of GT in two experimental models of natural aging. First, we investigate the effect on the estrous cycle, the Kisspeptin/GnRH neurons, and microglia cells in middle-aged female rats. We demonstrate that IGF1-GT prolongs rats' cyclicity, modulating Kisspeptin/GnRH secretion in the hypothalamus and modifying microglia cells number and reactivity. We propose to use IGF1-GT to delay reproductive senescence as a strategy for optimizing lifespan and combating aging-related health problems in women. Next, we studied the effects of IGF1-GT on microglial cells in 28 months old female rats. Aging presents a loss of brain homeostasis and chronic neuroinflammation, caused by senescent microglia. Therefore, it is of great interest to design strategies that allow modulating these glial cells' phenotype. We implemented IGF1-GT in 28 months old female rats, focused on the study of microglia in Striatum. IGF-GT influences microglia number, phagocytic activity and transcriptomic expression. These results suggest that IGF1-GT could modulate microglia activation and induces the microenvironment to neuronal survival. Our work supports the use of IGF1-GT as a tool to treat age related neural pathologies.

SYMPOSIA

Towards a molecular diagnosis of stress-related disorders. Fact or fiction?

Chairs: Melisa Carolina Monteleone / IIB-UNSAM. Marcela Brocco / Instituto de Investigaciones Biotecnológicas. UNSAM-IIBio-CONICET

The relationship between stress and the development of diseases is complex and the susceptibility to manifest them varies from person to person. Several studies indicate that, while short-term stress can be positive, chronic stress can be deleterious and has even been implicated in the pathophysiology of psychiatric disorders. Every day we are exposed to some type of stress, a situation aggravated by COVID 19 pandemic. Despite the prevalence of stress-related disorders, there are no standardized methods based on biochemical markers that could complement clinical evaluation in order to improve early diagnosis and treatment to apply. Hence, the search for readily accessible biomarkers of stress-induced disorders, e.g. circulating molecules and/or carried by extracellular vesicles, has gained popularity. While initial biomarker searches focused on neuronal molecules, in the last few years alternative sources were evaluated. Here, a specialist in Cognitive and Developmental Psychology will show us the importance of addressing mental health issues with particular focus on COVID-19 impact in the Argentinean population. Then, experts in the field of stress biomarker research from Chile, Mexico and Argentina will share their most recent findings and will show us how stress-induced alterations of the gut-brain axis functioning and of the inflammatory response could be exploited for biomarker discovery. Potential strategies to revert stress effects will also be discussed.

Evaluation of mental health during the pandemic in different samples of the Argentine population

JUAN CARLOS GODOY

Instituto de Investigaciones Psicológicas (IIPsi-UNC-CONICET)

In this presentation we will review the findings from various studies on the effects on mental health of the Social, Preventive and Obligatory Distancing (DISPO) established in Argentina in response to the COVID-19 pandemic. Specifically, results of cross-sectional and longitudinal studies carried out in samples of the general population, college students, and healthcare workers from different regions of this country will be presented. Taken together, these investigations underscore the need to promote systematic research on several aspects of mental health, integrating contributions from psychology and neurosciences, and favoring the development of better diagnostic markers for mental disorders, giving relevance to the research in the field of biomarkers of stress and related diseases.

Searching for novel therapeutic targets for the treatment of depression and metabolic risk: biomarkers for early life stress and intestinal dysbiosis

NAIMA LAJUD

Instituto Mexicano del Seguro Social

The relationship between stress and the development of diseases is complex and the susceptibility to manifest them varies from person to person. Several studies indicate that, while short-term stress can be positive, chronic stress can be deleterious and has even been implicated in the pathophysiology of psychiatric disorders. Every day we are exposed to some type of stress, a situation aggravated by COVID 19 pandemic. Despite the prevalence of stress-related disorders, there are no standardized methods based on biochemical markers that could complement clinical evaluation in order to improve early diagnosis and treatment to apply. Hence, the search for readily accessible biomarkers of stress-induced disorders, e.g. circulating molecules and/or carried by extracellular vesicles, has gained popularity. While initial biomarker

searches focused on neuronal molecules, in the last few years alternative sources were evaluated. Here, a specialist in Cognitive and Developmental Psychology will show us the importance of addressing mental health issues with particular focus on COVID-19 impact in the Argentinean population. Then, experts in the field of stress biomarker research from Chile, Mexico and Argentina will share their most recent findings and will show us how stress-induced alterations of the gut-brain axis functioning and of the inflammatory response could be exploited for biomarker discovery. Potential strategies to revert stress effects will also be discussed.

Towards a molecular diagnosis of stress-related disorders. Fact or fiction?

EUGENIO ANTONIO CARRERA SILVA

Instituto de Medicina Experimental (IMEX) - CONICET - Academia Nacional de Medicina

The relationship between stress and the development of diseases is complex and the susceptibility to manifest them varies from person to person. Several studies indicate that, while short-term stress can be positive, chronic stress can be deleterious and has even been implicated in the pathophysiology of psychiatric disorders. Every day we are exposed to some type of stress, a situation aggravated by COVID 19 pandemic. Despite the prevalence of stress-related disorders, there are no standardized methods based on biochemical markers that could complement clinical evaluation in order to improve early diagnosis and treatment to apply. Hence, the search for readily accessible biomarkers of stress-induced disorders, e.g. circulating molecules and/or carried by extracellular vesicles, has gained popularity. While initial biomarker searches focused on neuronal molecules, in the last few years alternative sources were evaluated. Here, a specialist in Cognitive and Developmental Psychology will show us the importance of addressing mental health issues with particular focus on COVID-19 impact in the Argentinean population. Then, experts in the field of stress biomarker research from Chile, Mexico and Argentina will share their most recent findings and will show us how stress-induced alterations of the gut-brain axis functioning and of the inflammatory response could be exploited for biomarker discovery. Potential strategies to revert stress effects will also be discussed.

Beyond astrocyte-derived extracellular vesicles as stress biomarkers: role in intestinal pathologies

URSULA WYNEKEN

Universidad de los Andes, Chile

Small extracellular vesicles (sEVs) have emerged as central players in intercellular communication. They are released by central nervous system cells, including neurons and astrocytes, and their bioactive cargo varies under different neurophysiological or pathological conditions, such as after exposure to stress. We have studied the transfer of astrocyte-derived sEVs to the blood and to peripheral organs. Besides typical sEV markers (such as CD63, TSG101, flotillin), astrocyte-derived sEVs collected from the blood contain proteins that are potential stress biomarkers. Moreover, the sEV proteome varies in different stress-related human psychiatric conditions (major depression, bipolar disorder). When tracking astrocyte-derived sEVs containing recombinant proteins in rats, we found that they are transferred to the gut-associated lymphoid tissue (GALT) in a manner depending on the presence of the gut-homing receptor CCR9. In stressed animals, the vein injection of astrocyte-derived sEVs rescues stress-induced intestinal inflammation. This novel astrocyte-to-gut axis appears to be relevant in regulating the GALT function. A dysfunction of this axis, e.g. under stress conditions, will contribute to the strong association between stress-related psychiatric conditions and intestinal pathologies. Acknowledgements: Fondecyt 1200693(UW) & 1211384 (LFB), Fondef ID19I10116 (UW)

ORAL COMMUNICATIONS

Memory and musical training in adolescents

María Angélica Benítez

Laboratorio Interdisciplinario de Neurociencia Cognitiva (LINC), Centro de Estudios Multidisciplinario en Sistemas Complejos y Ciencias del Cerebro (CEMSC3), Instituto de Ciencias Físicas (ICIFI), Escuela de Ciencia y Tecnología (ECyT), Universidad de San Martín (UNSAM), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)

The relationship between musical experience as well as general cognitive development throughout life has been widely studied. Studies have found that musicians achieved higher scores in memory tasks than non-musicians, but this was not investigated in the performance of emotional memory in adolescents' musicians and non-musicians. The goal of this study was to evaluate the relationship between musical experience, emotional and neutral memory in a sample of Argentinian adolescents. The performance of 30 adolescents between 12 and 15 years old, trained in Argentinian Conservatories of Music was compared to adolescents without this type of training in an emotional and neutral memory task (based on the International Affective Pictures System). They were evaluated on their free recall and recognition of the images, both immediately and deferred. The evaluations were carried out remotely due to publicly known sanitary restrictions. The results showed that the emotional material was more remembered than the neutral one. Immediately, no significant differences were found between the groups, however, it was found that the musicians remembered a greater number of images than the adolescents without musical training in the deferred measures (both neutral and emotional). Lastly, no significant differences were found in the recognition tasks. The results, of social, clinical, and educational implication, show that musical training modulates the emotional and neutral memory of adolescents.

Can video games enhance children and adolescents' cognitive capabilities? A systematic review of the transfer of video game training to cognitive and psychosocial abilities

Martina Boscolo

Laboratorio de Neurociencia, Universidad Torcuato Di Tella

Video games are extremely popular, especially among adolescents. Even though the effects they have on cognitive and psychosocial aspects have been widely studied, there is no consensus in the literature on the predominance of their beneficial or negative effects on children and adolescents' cognition. Evidence on this could shed some clarity on the potential of video games as educational resources to stimulate cognitive development. We conducted a revision on the effects that playing video games has on cognition in people under the age of 18, and considered its transfer to other aspects of life. After extensive search and filtering processes, 34 experimental and correlational studies were analysed. We found that certain video games positively affect executive functions, attention, memory, and decision making, among other cognitive capabilities. On the contrary, other video games are related to an increase in aggressiveness and risk-taking behavior and to a decrease in prosocial behavior. Moreover, various video games that have these effects are very popular and emerge as some of the most-downloaded and most-played nowadays. Given that playing video games might trigger experience-dependent plasticity, it is necessary to understand to which extent they affect cognitive development in ecological settings. This revision allows for a better comprehension of this research field. Key words: Video games, Cognition, Adolescence, Childhood, Transfer

A population dynamics model about how learning promotes adult neurogenesis in delimited regions of the zebrafish pallium.

Julio Roberto Castillo Elias

Laboratorio de Neurogénesis Adulta, Departamento de Fisica Médica, CNEA

Neural stem cells (NSCs) in the zebrafish pallium undergo through both symmetric and asymmetric divisions in order to generate new-born neurons and to perpetuate the NSC reservoir pool. A few studies address how the activity of neural circuits regulates the adult neurogenesis homeostasis, while the role of cognitive activity on new-born neuronal addition has not been explored yet. Here we aimed to test whether cognitive activity enhances adult neurogenesis by training zebrafish in a spatial relational task. We found that learning increases a ~3 fold NSC proliferation in the rostral-dorsomedial (rDm) pallium, when compared to mocked controls. Next we evaluated the role of learning on neuronal addition in the pallium. To do this, a cohort of proliferating NSCs were labeled by BrdU administration, and then fish were trained during 2 or 3 consecutive weeks. We found that training increases the number of newborn neurons in rDm proportional to the extent of cognitive activity. To understand the cellular mechanisms behind these results, we developed a population dynamic model of proliferating NSCs (based on Than-Trong el al 2020), where NSC proliferation and death are sensitive to cognitive activity. Our model suggests that learning in a spatial relational task promotes neurogenesis in rDm in two ways: firstly, by promoting newborn neurons' rescue from apoptosis due to network activity, and secondly, by acting as a catalyst for a successive labeled-NSCs proliferation.

Implausible alternatives paradoxically increase confidence in a perceptual decision

Nicolás Comay

Cognitive Science Group - Instituto de Investigaciones Psicológicas (IIPsi - CONICET - UNC)

Computational models of confidence in perceptual decisions predict that the presence of implausible alternatives in a decision making task should not affect reported confidence. However, research in non-perceptual tasks showed that implausible alternatives increase confidence, a counterintuitive finding that defies current understanding of confidence processes. Here we experimentally test whether this phenomenon also plays a role in perceptual decision making. We conducted 3 online experiments. In experiment 1 and 2 participants had to decide which of a set of stimuli was the biggest, and report their confidence level. In Exp1 half of the trials included very small, clearly incorrect stimuli, whereas in Exp2 one to three small alternatives were added. We found that the addition of implausible alternatives increased confidence. Moreover, confidence increased monotonically with the number of weak alternatives. In experiment 3 we aimed to replicate our findings in a different task; here confidence only increased minimally in correct trials. These results are hardly compatible with current computational models of confidence. Therefore, we proposed one alternative model that accounts for our data. Our work contributes to a thorough understanding of the cognitive processes underlying our sense of confidence, and proposes venues for future research.

What can non-linear embeddings tell us about the way a mouse learns a motor skill?

Alvaro Concha Alvarez Prado

Neurobiology of Movement Lab, Medical Physics Dept, Instituto Balseiro, UNCUYO-CNEA

Animals exhibit complex behavioral repertoires that can be described as combinations from a finite set of stereotyped movements. Behavioral responses are flexible, since different movement sequences can be used to solve similar tasks, and are adaptable to changing environments through learning mechanisms. Given its adaptability and flexibility, translating animal behavior into quantifiable movement sequences can be challenging. On the one hand, manual classification can be time-consuming and not reproducible between subjects. On the other hand, heuristically created categories tend to ignore inherent information regarding intra- and inter-animal variability, frequently found in unrestrained behavior. In addition, a quantitative description of animal behavior is required to understand how the brain encodes particular behaviors, what are the underlying neural circuits and how these circuits are modified during motor learning. In this work, we used unsupervised machine learning techniques to classify different types of movements executed by mice performing a motor skill learning task (accelerating rotarod). We used UMAP embeddings to find a low dimensional representation of mouse behavior. We then clustered these behaviors into separate categories and associated them with specific movement sequences and learning stages. In this way, we shed light on the underlying structure of animal behavior, improving our understanding of the learning dynamics of a new motor skill.

Assessing the object recognition memory dynamic network upon retrosplenial cortex inactivation- a functional neuroimaging study in rats

Ana Belén de Landeta

1 Laboratorio de Memoria, Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis" (IBCN), CONICET-Universidad de Buenos Aires, Buenos Aires, Argentina 2 Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

Little is known about the object recognition memory (ORM) network. We recently found that the retrosplenial cortex (RSC) is required for ORM consolidation and retrieval; yet RSC inactivation during acquisition prevents its requirement for these memory stages, suggesting that ORM network changes. To assess this we used cerebral blood flow (CBF) SPECT for imaging rats brain activity patterns during habituation (H), training (TR), test (TS, 24h) and re-test (reTS, 7d after TR) in 2 groups; rats infused with saline (control, Ctl) or muscimol (Musc, GABA A agonist, 0.1 µg/side) into the RSC 15min before TR. Within group comparison showed that CBF during TR compared to H decreased over the midline cortical regions from prefrontal cortex to the RSC. Also, CBF increased during TR in the lateral hypothalamus and superior colliculus. During TS compared to TR, CBF increased in the piriform and lateral entorhinal cortex. When compared reTS to TS, CBF decreased in the anterior cingulate cortex and the ventral thalamic nuclei. The deactivation of RSC during TR was stronger in the Musc group, but the largest differences between groups were found during TS. In this condition, CBF in the orbitofrontal cortex and dorsal hippocampus decreased in the Musc group, while CBF in the RSC was higher in this group. We uncovered complex brain-wide activation patterns in the different stages of ORM and showed that RSC inactivation during memory acquisition changed the memory network during retrieval.

Effects of elevated episodic alcohol consumption during adolescence on recognition memory

Rodrigo Manuel García-Virgolini

Facultad de Psicología; Universidad Nacional de Córdoba

Adolescent alcohol consumption is an important health issue in Argentina. Many studies indicate that age of first intoxication is more relevant than age of first contact in explaining alcohol related disorders. This suggests that preclinical studies should focus on models that generate high amounts of consumption in a short time. The present study assessed in male and female Wistar rats the effects of chronic exposure to alcohol during adolescence on recognition memory, with a model simulating elevated episodic alcohol consumption (EEAC). The hypothesis was that exposure to EEAC would result in significant deficits in recognition memory. 48 rats were submitted to a protocol of daily intermittent 2 hour sessions of alcohol auto-administration (EtOH 10%) during adolescence from postnatal days 30-50. Control group received water. Between postnatal days 60-67 rats were evaluated with novel object recognition test. Rats exposed to alcohol during adolescence exhibited significantly less distance traveled in experimental arena [F(1,44)=4.82; p=0.03]. However, no alcohol induced deficits were observed on novel object discrimination. Furthermore, rats that had undergone EEAC showed slight but significant increase in novelty discrimination compared to controls [F(1,44)=4.21; p=0.04]. The hypothesis that EEAC would impair recognition memory was not confirmed. Nonetheless, less distance traveled by animals exposed to EEAC suggests the procedure may have altered motivational patterns.

Impairment of aversive episodic memories during Covid-19 pandemic: The impact of emotional context on memory processes

Candela Sofia Leon

Laboratorio de Sueño y Memoria/Instituto Tecnológico de Buenos Aires

Episodic memory is the ability to recall about what, where and when the event happened. Furthermore, there is a consensus that pleasant or aversive events are better remembered than neutral events and that episodic memory processes are modulated by anxiety and depression. People's mental health has deteriorated due to the COVID-19 pandemic, showing a growth in anxiety and depressive symptoms. Here, we hypothesize that the increase in negative symptoms modifies the ability to encode and consolidate memories. To study this, we evaluated the effects of emotional context on encoding and consolidation of aversive and neutral episodic memories.

Dissociated neural mechanisms for executive and arousal vigilance

Fernando Gabriel Luna

Instituto de Investigaciones Psicológicas (IIPsi, CONICET-UNC), Facultad de Psicología, Universidad Nacional de Córdoba, Argentina

Vigilance is the challenging ability to sustain attention during long periods. Recently, it has been proposed that vigilance is better understood as two dissociated components: (a) executive vigilance, a cognitive component implied in detecting infrequent critical signals; and (b) arousal vigilance, a rather automatic component involved in sustaining fast responses to stimuli from environment. The present study aimed at dissociating the neural mechanisms of the executive and arousal vigilance components. 37 participants (age: M = 25.86; SD = 4.99) completed two experimental sessions, in which the ANTI-Vea task (i.e., a continuous behavioral task of ~38 min suitable for simultaneously measuring vigilance components) was performed while EEG signal was recorded. Dissociated neural responses were observed for vigilance components. For executive vigilance, correct detections were anticipated by a decline in alpha power prior to the infrequent critical signal appearance. Instead, for arousal vigilance, fastest responses were anticipated by a reduced delta power prior to stimuli appearance. Moreover, while the executive vigilance decrement was observed as a change on late event-related potentials (i.e., P3 and slow positivity), the slowness on arousal vigilance responses was found as a change in P2, a rather earlier event-related potential. Altogether, this study presents a novel dissociation of the neural mechanisms associated with vigilance components.

Non-Linear susceptibility to interferences in declarative memory information

Malen Daiana Moyano

Laboratorio Sueño y Memoria, Dpto Ciencias de la Vida, ITBA

After encoding, memories go through a labile state followed by a stabilization process known as consolidation. Once consolidated they can enter a new labile state after the presentation of a reminder of the original memory, followed by a period of re-stabilization (reconsolidation). During these periods of lability the memory traces can be modified. Currently, there are studies that show a rapid stabilization after 30 min, while others show that stabilization occurs after longer periods (e.g. 6 h). Here we investigate the effect of an interference treatment on declarative memory consolidation, comparing distinct time intervals after acquisition. On day 1, participants learned a list of non- syllable pairs (List 1). Immediately after, 30 min, 3 h or 8 h later, they received an interference list (List 2) that acted as an amnesic agent. On day 2 (48 h after training) participants had to recall List 1 first, followed by List 2. We found that the List 1 memory was susceptible to interference when the List 2 was administered immediately or 3 h after learning; however, shortly after acquisition (e.g. 30 min) the List 1 memory becomes transiently protected against interference. We propose the possibility that this rapid memory protection could be induced by a fast and transient neocortical integration becoming partially independent from the hippocampus followed by a hippocampal re-engagement where the memory becomes susceptible to interferences again.

Gestational environmental enrichment affects offspring behavior of adolescent rats in a sex specific manner: A preliminary investigation

Ana Paula Toselli

Cátedra de Fisiología Animal - Facultad de Ciencias Exactas, Físicas y Naturales - UNC

The maternal environment is important for embryonic brain development. We investigated whether environmental enrichment during the gestation period influences offspring behaviors in juvenile male and female rats. Pregnant rats (from gestation day 1 to 20) were housed in an enriched environment (EE) consisting of large cages for exploration, stimulating toys, running wheels and eight companions for social interaction. A control group was housed in standard cages (two per cage). After birth, litters from both groups were maintained in a standard environment until 45 postnatal day. The effects of maternal enrichment on the behavior of male and female offspring were determined by elevated plus maze (EPM), open-field (OF) and social preference test (SPT). The results showed that in EPM, female offspring of EE mothers spent more percentage of time in open arms indicating a decrease in anxiety-like behavior. In OF, male and female EE rats showed more locomotor activity and spent more time in the aversive inner zone of the maze than control rats, indicating lower emotional reactivity behavior. When examining social behavior, there is a preference for investigating the social stimulus over the object stimulus in all groups. However, EE males exhibit less time spent investigating the social stimulus compared to control males. The evidence demonstrates that maternal exposure to EE affects the behavioral trajectories of offspring in a sex-specific manner.

Can Tourette syndrome phenotypes be induced by acutely inhibiting Nkx2.1 derived striatal interneurons?

Camila Coll

Instituto de Fisiología y Biofísica Bernardo Houssay (IFIBIO)

Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics. Most patients also present comorbid conditions like OCD and ADHD. TS pathophysiology remains poorly understood, however, the number of PV+, nNOS+ and ChAT+ striatal interneurons (SIs), which all derive from cell precursors expressing the transcription factor Nkx2.1, is reduced in the brain of TS patients. In previous studies, where we achieved a combined ablation of SIs, lesioned mice developed abnormal involuntary movements resembling motor tics and also behaviors reminiscent of common comorbid conditions, including an increase in stereotypies, locomotion, and spontaneous repetitive behaviors. Nonetheless, ablations give time

for plastic compensations to occur, which brings to the question, can these phenotypes be induced by acutely inhibiting the SIs, or only after an ablation? To get a transient inhibition of the SIs, we injected Nkx2.1-Cre mice intrastriatally with an AAV-h4MDi-mCherry-DIO, to selectively express in SIs a modified inhibitory muscarinic receptor that can be pharmacologically activated by clozapine-N-oxide (CNO). Our preliminary results show that about 25% of the transfected mice show abnormal movements when after intraperitoneal administration of CNO, although less marked than those observed after SI ablation. Moreover, inhibition of SIs increased locomotion and spontaneous repetitive behaviors. Further studies are needed to confirm these findings.

Second wave of Covid 19 pandemic in Argentinian population: vaccination results in a decrease in depressive symptoms

Celina Goyeneche

Laboratorio de Memoria, Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis" (IBCN), Facultad de Medicina, UBA-CONICET

Covid-19 is a disease caused by the coronavirus SARS-CoV-2. So far, up to May 2021 it has caused 4.42 million deaths on the planet and 110,000 originated in Argentina. In addition to the many physical illnesses directly associated with the Covid-19, it also causes psychological disorders such as depression and anxiety. In this work, we studied the progression of the self-perceived levels of generalized anxiety disorders (GAD) and depression in two adults groups with 18-30 and 31-50 years old. Both of them were surveyed during the first (November 2020) and the second (May 2021) waves of the SARS-CoV-2 outbreak, in the Buenos Aires Metropolitan Area, Argentina. We used the PHQ-9 and GAD-7 tests to evaluate depression symptoms and GAD levels. We also asked about weekly physical activity and the vaccination status to analyze their impact as possible protective factors of the population's mental health after such a prolonged period of pandemic. Our data show that in both age groups, GAD increased during the second wave, while depression decreased. These tendencies are valid for both men and women. We also found a positive correlation between generalized anxiety and depression in both waves. Vaccination showed no significant effect in GAD, but a decrease in depression levels for the 31-50 group. In concordance with our previous works, physical activity seems to act as a protective factor that mitigates GAD and depression levels.

Region-specific features of early microglial activation in a conditional mouse model of TDP-43 proteinopathies

Gabriela Verónica Nieva

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Microglia-driven neuroinflammation can play an important role in the pathophysiology of neurodegenerative disorders. We have shown that transgenic mice conditionally overexpressing human nuclear wild-type TDP-43 protein (hTDP-43-WT) in forebrain neurons, recapitulate key features of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). After 1 month expression of the transgene, this mouse model displays impairment in cognitive and social behaviors in the absence of motor abnormalities. We previously described early-stage microglial activation in these mice by analyzing fold change in percentage of Iba1+ area in selected cortical and hippocampal regions. To extend these previous findings, we now performed a quantitative assessment of microglial morphology using Iba1 immunofluorescence. We found an increased number of Iba-1-labelled microglia in motor cortex (MC), in addition to longer perimeter and larger soma size in prefrontal (PFC), somatosensory (SSC) and motor cortices. Sholl analysis of microglia from MC and SSC revealed a reduction in branch complexity as we found a decrease in total process length, fewer total intersections and a significant decrement in branching 16–20 µm away from the soma, compared to control mice. In sum, these results detailing microglial morphological features expand our understanding of the relationship between early-stage neuroinflammatory processes and behavioral deficits in TDP-43 animal models of FTD/ALS.

Altered beta bursts in the motor cortex after dopamine depletion and levodopa medication in a rodent model of Parkinson's disease

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The nigrostriatal degeneration developed during Parkinson's disease (PD) leads to changes in basal ganglia functioning that ultimately impacts the motor cortex; leading to abnormal patterns of neuronal oscillations that emerge in the primary motor cortex (M1) after dopamine depletion and during dyskinesia associated to chronic treatment with levodopa, which is the gold standard antiparkinsonian medication. Using electrophysiological single unit and local field potential recordings from mice model of PD, we identified the altered properties of M1 beta bursts (15–35 Hz) that have a significant association with motor impairment in PD. We also demonstrated that beta persistence is related to slow movement initiation in the parkinsonian condition. Furthermore, we unraveled how pathological beta activity is modulated during the time-course of levodopa administration and its relationship with gamma oscillations (60-95 Hz); resulting the gamma amplitude modulation by beta phase as the hallmark of the symptomatic "off" medication state.

Temporal assessment of behavioural alterations and sex influence in an NMDA receptor knockout model of schizophrenia.

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Schizophrenia (SZ) is a chronic mental disorder frequently emerging between adolescence and adulthood and encompassing various symptomatic domains. It affects both males and females but clinical differences have been observed. Although the etiology of SZ is still misunderstood, alterations of GABAergic interneurons (INs) are considered to be pathophysiologically relevant since alterations in cortical INs expressing parvalbumin (PVs) have been found in patients. Normal wiring of cortical circuits relies on the proper postnatal maturation of PVs; thus, alterations of these INs could be related to the neurodevelopmental aspect of SZ. We have shown that ablation of NMDA receptors in cortical GABAergic INs from mice at early postnatal age results in SZ-like phenotypes that emerge during adulthood. However, their precise trajectory had not been fully described and sex differences were not assessed. Here, we characterized the time course of behavioral phenotypes (P25-150), evaluating sex differences and presymptomatic stages. As expected, behavioral phenotypes in male KO mice emerged once adolescence was completed, but female KO mice displayed a more complex trajectory, with transient impairments in Y-maze spontaneous alternation before adolescence and abnormal marble burying responses around the transition from adolescence to adulthood. Thus, while the majority of SZ-related phenotypes emerge in adulthood, specific traits may be present at early stages in a sex-specific manner.

Growth hormone secretagogue receptor is required to enhance reward-related behaviors adaptations toward palatable stimuli in calorie-restricted mice

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Ghrelin is a stomach-derived hormone that acts via growth hormone secretagogue receptor (GHSR). GHSR is expressed in the mesolimbic pathway, especially in the ventral tegmental area (VTA) that innervates the nucleus accumbens (Acb). Since plasma ghrelin levels increase under calorie restriction, GHSR signaling could act in the mesolimbic pathway and affect reward-related behavioral adaptations. We investigate the cFos neuronal activation marker induction in the mesolimbic pathway as well as the saccharine consumption in wild-type (WT) mice and GHSR-deficient mice during a 5-day 60% calorie restriction protocol. GHSR-deficient mice showed: 1) a more severe weight loss and hypoglycemia, 2) a similar increase of

cFos in the VTA but a smaller increase of cFos in the Acb, and 3) a reduced overconsumption of saccharin, than WT mice during the calorie restriction protocol. When CR mice were refed, we found that GHSR-deficient and WT mice did not show different hyperphagia or glycaemia but GHSR-deficient mice show reduced saccharine consumption as compared to WT mice. Thus, we conclude that GHSR plays a main role during, and after, a calorie restriction condition. In particular, we found GHSR seems to be required for the maintenance of energy balance and glucose homeostasis as well as for the full calorie restriction-induced activation of the reward-related brain centers and saccharine overconsumption during and after calorie restriction.

Low frequency brain representation of acoustic features during goal oriented dialogue

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During dialogue, speakers rapidly process different aspects of speech in order to respond and continue engaged. In particular, acoustic/prosodic features encode different intentions and emotions, allowing a fluent communication. The aim of this work is to better understand how the speech envelope and the voice pitch from the preceding 500 ms are encoded in the brain. Previous studies explore these features in highly constrained contexts and stimuli, such as pre-recorded sentences or radio monologues. Here, we analyse electroencephalography (EEG) data and audio recordings from pairs of participants engaged in unconstrained dialogue while performing collaborative tasks. Overall, our results follow very similar patterns to previous work but in a novel, less constrained scenario. By inspecting brain activity oscillations, we observe that the information contained in these features is encoded mainly in the low-frequency EEG bands (delta: [1 4]Hz and theta: [4 8]Hz) with a latency lower than 300 ms. Moreover, we show a better performance in predicting the EEG signal than previous studies, in particular in the frontal electrodes, with correlation values between prediction and signal of up to 0.3, suggesting that these features become even more relevant during natural speech. The present work paves the way for studying brain representations of more complex aspects of speech in natural context, such as phonological features or speech acts characteristics.

Diagnostic Performance of MRI Volumetry in Epilepsy Patients With Hippocampal Sclerosis Supported Through a Random Forest Automatic Classification Algorithm

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Introduction:Many methods offer volumetry services for MR data used to assist in clinical diagnosis of hippocampal sclerosis (HS).Association between severity of histopathological anomalies and hippocampal volumes was reported using MR volumetry with a higher diagnostic yield than visual examination. Interpretation of volumetry is challenging due to methodological differences and variability of hippocampal volume.We aimed to quantify diagnostic yield from two techniques: FreeSurfer v.06 and volBrain-HIPS. Methods:Volumetry measures were calculated using MRI from 61 healthy controls and 57 patients with unilateral HS.We validated the results by a machine learning classification algorithm (Random Forest) computing accuracy and feature relevance to distinguish between patients and controls.Mean reference values and 95% confidence intervals were calculated for left and right hippocampi along with hippocampal asymmetry to test diagnostic accuracy. Results:Bothmethods showed excellent classification performance (AUC:> 0.914) with differences in absolute (cm3) and normalized volumes. Hippocampal asymmetry was the most accurate discriminator from all estimates (AUC:1~0.97). Similar results were achieved in the validation test with an automatic classifier (AUC:>0.960). Conclusion:We calculated reference volumetry values from two methods to accurately identify patients with HS. Validation with an automatic classifier confirmed the principal role of the hippocampus for diagnosis.

Assesing the usefulness of an optogenetics setup to study the circadian clock of Drosophila melanogaster

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Light-triggered neural activation, or optogenetics allows the manipulation of neural activity with millisecond precision. The simplest protocol is to express, light-gated ion channel in neurons of interest. We built an optogenetic setup to study neural circuits that control the circadian clocks in flies. As Drosophila, is supposed to be blind to red-shifted wavelengths, in this work we employed Chrimson, a red-shift ChR2 variant, to in vivo activate neurons without disturbing the circadian rhythms. By expressing Chrimson in fruitless neurons we were able to activate courtship movements in males, proving the functionality of this system in our hands. Next, we quantified neuronal activation at different wavelengths, intensities and stimulation times, employing the courtship behavior as a readout. We found that high light intensities were needed to evoke behavioral changes. Then, as DN1p neurons control sleep and circadian rhythms, we drove the expression of Chrimson onto these neurons. Surprisingly, we observed a clear increase in locomotor activity of control flies during light pulses, suggesting that these flies can see red light. This increase of activity is much less pronounced in flies expressing Chrimson, which suggests that the opening of the channels partially suppresses the activity increase. Thus, even though our results may support earlier findings, they also cast some doubts on the usefulness of Chrimson as an optogenetic tool to study the neural control of sleep.

Benchmarking human visual search computational models in natural scenes: models comparison and reference datasets

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Nowadays, several algorithms are able to predict gaze positions during simple observation, but few models attempt to simulate human behavior during visual search in natural scenes. Moreover, these models vary widely in their design and exhibit differences in the configuration of their datasets and metrics employed. Thus, there is a need for a reference point, on which each model can be tested, and from where potential improvements to the algorithms can be derived.

Three models were considered: a Bayesian model (cIBS), one based on a CNN (IVSN), and one based on reinforcement learning (IRL). Each of them had its own dataset and was evaluated on all of them. The analysis was centered on performance and similarity to humans.

Not surprisingly, each model performed best on its own dataset. However, cIBS displayed the greatest similarity to humans in all of them. IRL performs categorical visual search and, thus, generalized poorly to other datasets. IVSN was great at finding objects, but failed to capture human behavior. Interestingly, human observers didn't display common distractions, such as looking at human faces, but cIBS did. Furthermore, humans are strongly guided by context, whereas the models ignore where objects are commonly located in a scene.

Incorporating the context of a scene seems to be crucial for capturing human behavior. The present work shows the urgency for common metrics and datasets for the development of more general visual search models in natural scenes.

Deletion of the vesicular GABA transporter from NeuromedinS+ SCN neurons impairs behavioral circadian rhythms in mice.

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In mammals, the suprachiasmatic nuclei of the hypothalamus (SCN) houses the master circadian clock. The SCN in rodents consists of approximately 20,000 neurons, and among the multiple peptides and neurotransmitters expressed in the SCN, GABA is the most prevalent. While GABA has been shown to be involved in the coupling between SCN cellular oscillators it is not clear whether GABAergic transmission within the nucleus is essential to sustain circadian rhythms. In the present study, we used targeted mutagenesis to knock out the vesicular GABA transporter (Vgat) from NeuromedinS (NMS+) neurons in the SCN of mice. While all mice carrying the homozygous deletion of Vgat in the NMS+ cells of the SCN (Nms-Vgat-/-) were able to synchronize their wheel-running activity to a normal light-dark cycle, 60% of them failed to show circadian activity patterns after being switched to constant darkness. Nms-Vgat-/- mice showed the expected decreased VGAT expression in the SCN as well as decreased expression and altered distribution of the neuropeptide VIP, which is critical for normal SCN function. Furthermore, when the persistency of the rhythmic expression of clock genes in ex-vivo SCN explants was evaluated through Per2-luciferase expression, Nms-Vgat-/- mice showed faster damping of the oscillations. Taken together our data suggest that GABA signaling may have a critical role in the orchestration of behavioral circadian rhythms and the development of SCN neuronal network properties.

Temporal reversibility of neural dynamics as a signature of consciousness

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The brain is capable of constructing representations of the world including the direction of time. In this work, we investigated whether this can be decoded from electrocorticography (ECoG) recordings in non-human primates in different states of consciousness (awake, sleep and ketamine). Time courses of the principal components (PC) of the data were transformed to frequency and phase spectrograms and used as the input of a convolutional network trained to distinguish original vs. time reversed epochs. In total, 16,200 models were fitted for 81 conditions (3 levels of model complexity, 3 types of data, 3 PCs, in 3 states of consciousness) with 100 iterations each. This was repeated after randomizing data labels to construct a null model. Unshuffled models yielded a significantly higher performance ($p < 0.001$). For wakefulness, the AUC in the validation set was always above .75. In the case of sleep, the best performance was observed for the models that included the phase information. For the ketamine condition, significant performance was observed for the most complex models. In the frequency domain, a greater relative importance was observed for high frequencies. Particularly in sleep, the importance was highest for the phase data. In summary, deep convolutional network models were able to predict the direction of time from ECoG data during wakefulness, but this prediction was hindered in states of reduced awareness such as deep sleep or under ketamine anesthesia.

The impact of glial signals on neuronal structural plasticity

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Recently, we described that a functional glial clock is necessary for circadian plasticity in the small lateral ventral neurons (sLNvs), a group of key pacemaker neurons of D. melanogaster. Circadian structural plasticity involves rhythmic changes in the degree of arborization and fasciculation of their dorsal termini. The sLNvs

express PDF, a neuropeptide relevant in the synchronization of the clock network that oscillates in phase with this remodelling process. We have previously demonstrated that circadian plasticity modifies the way the pacemaker circuitry is wired regularly, but its impact on behaviour and the molecular basis that control this process are yet to be defined. Building upon our previous results, we examine in depth the impact of neuronal-glial connectivity. Using GFP reconstitution analysis (GRASP), we found that sLNv termini contact directly with two different glial subtypes (astrocyte-like and ensheathing glia) and that these contacts are time-of-the-day dependent. Interestingly, blocking adult glio-transmission has different effects on PDF levels and plasticity depending on the type of glia recruited and the length of the treatment (12 or 24 hours). Additionally, preliminary experiments show that preventing clock oscillations in different glial subtypes affect circadian plasticity distinctively. Taken together, our results suggest a complex glial implication in the modulation of adult structural plasticity with distinct roles for different glial subty

The role of orsai in circadian rhythms

Giovanna Margarita Velázquez Campos

Genética del comportamiento, Fundación Instituto Leloir

Rhythmic rest-activity cycles are controlled by an endogenous clock. In Drosophila, the circadian network resides in about 150 neurons organized in groups, out of which the group of ventral lateral neurons (LNv) is essential in the control of rest-activity cycles. Previous results from our laboratory suggest that chronic orsai dysregulation (osi, an important gene in lipid catabolism) within the LNvs affects circadian patterns of locomotor activity in young and aged flies. To understand osi ´s role in the adult brain, genetic tools were used to downregulate osi levels in an adult-specific way, and thus evaluate the impact of osi on the clock neurons. We show that adult-specific osi knockdown in LNv neurons lengthens the period and reduce the consolidation of circadian locomotor activity patterns in young flies. Concomitant expression of its human ortholog ETFRF1 rescues the period phenotype observed. Moreover, ETFRF1 expression in the context of OSI knockdown in aged animals results in flies with properties reminiscent of younger individuals. In addition, decreasing osi levels in this key group of circadian neurons affects the morning anticipation both in young and aged groups under daily conditions, likely through the modulation of PDF levels. Together these results suggest that osi plays a fundamental role in LNv physiology.

FREQUENCY AND EMOTIONAL PRIMING COULD MODULATE COMPLEX DECISION-MAKING PROCESSES DEPENDING ON TASK RELEVANCE

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Complex decision-making processes (CDM) differ from simple ones because they require greater cognitive commitment and higher response time (RT). We evaluated in previous cognitive experiments if repetition (RP) and emotional priming (EP) modulate CDM by presenting faces (4) sequentially, with different frequencies (1, 6 or 12 repetitions) in RP experiments or associated with one emotional content phrase (positive, negative or neutral) in EP ones. Subjects were randomly divided into 2 groups by asking them to choose a face to realize an important task (IT) or without specifying the task (NST). Results indicated that CDM processes could be modulated by both priming when the task was not specified (NST group), but not when the choice was made to do an important task (IT group), when RT was higher. These experiments raise the role of the task´s nature in a possible top-down mechanism modulating CDM. Here we analyse a third group, asked to choose a face to realize a not important task (NIT), replicating the same online experiments and compared to a new NST group. Results show that: 1. When RP was assessed, the face with frequency 12 was significantly more chosen in NST than in NIT and RT in NIT is significantly longer than NST; 2. When EP was evaluated, NIT group has chosen more significantly faces associated with negative or neutral phrases (than positive and than NST group). These results support the hypothesis that priming modulation could be affected by the task´s relevance.

Consolidated Aversive Memories are hard to forget

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Although it has been demonstrated the existence of active forgetting (AF) for several acquired experiences, there is poor evidence about this process for consolidated aversive memories (CAMs). Previously, we have shown that blockade of D1 receptors in the ventral tegmental area (VTA) or positive allosteric modulation of GABAA receptors in the hippocampus (HP) or via systemic administration do not cause AF of CAMs in rats. Here we first decided to extend our analysis on the role of GABAergic system administering a low dose of a specific agonist. Neither the infusion of muscimol in the HP nor in the VTA after inhibitory avoidance (IA) training modified the duration of this memory. Then, based on previous and controversial studies, we next decided to assess the role of the GTPase Rac1 in AF. Our results show that post-retrieval inhibition of this protein by NSC23766 infusion in the HP or the VTA of male and female rats did not affect the maintenance of IA memory. So far, our results do not support the participation of D1 receptors nor GABAA receptors nor Rac1 in an AF mechanism for CAMs in the HP or the VTA. One explanation could be that we are failing to find the correct pathway/region where AF is occurring. Other possibility indicates that AF might not dictate the fate of CAMs. Since these memories are strongly relevant for individual's survival, the lack of AF controlling its persistence could have adaptive implications.

Coordination of neural activity across segments

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In animal motor behaviors, the segments along the antero-posterior axis perform movements in a coordinated manner. Leeches are an outstanding model to analyze the underlying neuronal network controlling this function because the 21 segments that compose the body are virtually identical, simplifying the question on intersegmental coordination to that on interactions among iterated units. Leeches crawl over solid surfaces through a succession of elongation and contraction body waves, anchored on the posterior and anterior suckers. Each segment bears all the neurons required to produce this rhythmic motor pattern and dopamine evokes fictive crawling in isolated midbody ganglia. The rhythmic motor pattern can be also elicited in chains of three ganglia in a coordinated way. The activity pattern in both experimental conditions is highly similar, and fits behavioral parameters. To analyze the degree of interaction of the local segments along the chain we manipulated the membrane potential of the premotor nonspiking neurons. A hyperpolarization of this neuron that in isolated ganglia annuls the crawling motor pattern, produces a minor slowdown in the chain. The results indicate that isolated short ganglion chains have all the elements necessary to produce coordinated activity, but the network cannot be considered as a series of interacting autonomous segmental units. Within the chain, the segmental networks are integrated in a global network that subdues the segmental units.

Audiovisual integration in the Mauthner cell enhances escape probability and reduces response latency

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Fast and accurate threat detection is critically important for animal survival. Reducing perceptual ambiguity by integrating multiple sources of sensory information can enhance threat detection and reduce response latency. However, studies showing a direct link between behavioral correlates of multisensory integration and its underlying neural basis are rare. In fish, an explosive escape behavior known as C-start is driven by an identified neural circuit centered on the Mauthner cell. The Mauthner cell can trigger C-starts in response to visual and auditory stimuli allowing to investigate how multisensory integration in a single neuron affects behavioral outcome after threat detection. Here we demonstrate that in goldfish visual looms and brief auditory stimuli can be integrated to increase C-start probability and that this enhancement is inversely correlated to the saliency of the cues with weaker auditory cues producing a proportionally stronger multisensory effect. We also show that multisensory stimuli reduce response latency locked to the presentation of the auditory cue. Finally, we make a direct link between behavioral data and its underlying neural mechanism by reproducing empirical data with an integrate-and-fire computational model of the Mauthner cell.

Remapping of CA3 ensembles induced by optogenetic stimulation of young but not mature adult-born granule cells in free-foraging mice

Matias Mugnaini

Fundacion Instituto Leloir (IIBBA)

Hippocampal adult-born granule cells (aGCs) are transiently hyperplastic and excitable around developmental week 4, and reach a mature physiology around week 10. While the activity of aGCs during this transition has been characterized, its influence on their main target CA3 is still poorly understood. In this work, we studied the impact of optically stimulating young (4 weeks) or mature (8 weeks) cohorts of aGCs expressing channelrhodopsin-2 on the electrophysiology of downstream CA3 neurons in free foraging mice. The early evoked response (onset: 5-13 ms) of individual CA3 cells was similar for both cohorts, although mature aGCs recruited more postsynaptic neurons (3 vs 14 %). In addition, a subset of CA3 cells presented a conspicuous late-onset response that was evoked exclusively by mature aGC stimulation. We also investigated if repeated optogenetic stimulation might alter stable CA3 spatial maps built in a familiar arena. We found significant remapping in the proximal half of CA3 when stimulating young but not mature aGCs. The same manipulation 2 days later did not induce remapping, suggesting a strong one-shot plasticity phenomenon. Our results are in line with the proposed role of adult hippocampal neurogenesis in spatial discrimination. The continuous addition of cells capable of triggering one-shot remapping could be a key mechanism for the encoding of new episodic memories without mutual interference in downstream CA3 networks.

Neuronal Networks: Balancing Motor Outputs

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The execution of rhythmic motor behaviors requires multiple control mechanisms to adjust the behavioral output, narrowing down the degrees of freedom of a system with multiple active units. Leeches crawl on solid surfaces through a succession of elongation and contraction body waves, anchored on the posterior and anterior suckers. Each segmental ganglion contains all the neurons required to produce this rhythmic motor pattern, and dopamine evokes fictive crawling in isolated midbody ganglia. The pair of premotor NS (nonspiking) neurons are connected to motoneurons through a central network that provides recurrent inhibitory signals onto the motoneurons. We aim at understanding the role of NS in the context of crawling. During fictive crawling NS neurons receive inhibitory signals, tuned to the contraction phase of crawling, monitored through the DE-3 motoneuron. The results suggest that the inhibitory signals in NS are delivered by the rhythmogenic circuit that controls the motoneuron output. Thus, excitatory signals to DE-3 are correlated to inhibitory signals in NS that, in turn, can restrict the motoneuron activity. To this point the data indicates that the premotor NS neuron acts as an homeostatic element, restricting the motor output. Our future work will determine if this is a global effect onto the motoneuron population or whether it is directed to specific motoneurons, sculpturing the motor pattern.

Signaling pathways mediated by CRHR2α in neuronal cell contexts

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The corticotropin-releasing hormone (CRH) system, its ligands (CRH and urocortins 1-3) and receptors (CRHR1 and CRHR2) drive the response and adaptation to stress. Dysregulation of the CRH system is causally linked to stress-related psychiatric disorders. The CRHR2α splice variant, the main isoform in the mouse brain, has an

uncleavable signal peptide giving this receptor special trafficking and signaling features. Our aim is to characterize UCNs/CRHR2α signaling pathways in a neuronal context using the hippocampal cell line HT22 stably expressing the receptor (HT22-CRHR2α) and primary neuronal cultures. ERK1/2, CREB and Akt were activated downstream CRHR2α in HT22-CRHR2α cells. ERK1/2 and CREB activation depended on cAMP generated by the soluble adenylyl cyclase (sAC) and transmembrane adenylyl cyclases but only sAC was required for Akt activation. Upon stimulation, HT22-CRHR2α cells undergo morphological changes that required sAC-produced cAMP and PKA activation independently of ERK1/2 activation. We observed an unusual trafficking for the CRHR2α due to the pseudo-signal peptide: the fraction of the receptor in the cell surface increased 6 min after stimulation returning to basal levels after 30 min. In primary neurons, preliminary results suggest that Fos induction by the CRH system may depend on neuronal activation and the ligand used. Our results highlight the relevance of cellular contexts and provide information to define the role of UCNs and CRHR2α in the CRH system.

A Functional Interaction Between a Region of the SARS-CoV-2 Spike Protein and the Human α7 Nicotinic Receptor

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Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The binding of the viral spike protein (S) to angiotensin-converting enzyme 2 in host cells is crucial for infection. The S protein has been suggested to interact with nicotinic acetylcholine receptors (nAChRs), and their contribution to the COVID-19 inflammatory pathophysiology has been proposed. α7 is an interesting candidate target because it is present in neuronal and non-neuronal cells, and it has neuroprotective and anti-inflammatory actions. By whole-cell and single-channel recordings we revealed that the Y674-R685 region of the S protein shows a direct functional interaction with human α7 nAChR. The S fragment exerts a dual effect, acting as a low-efficacy agonist and a non-competitive antagonist. In agreement with molecular dynamics simulations showing stable binding of this region to the ACh binding pocket, the S fragment activates α7, but only in the presence of a potentiator, supporting its action as a very low-efficacy agonist. In addition, it allosterically inhibits α7 responses elicited by ACh, which may result in the predominant effect. This study provides unequivocal evidence supporting a functional α7-S protein interaction, which may play a role in infectivity and/or disease progression and may be explored for new therapeutic opportunities.

Effects of the antipsychotic drug chlorpromazine on D1/D5R constitutive activity and postsynaptic currents in prefrontal cortex (PFC) neurons

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The PFC is a key associative cortical region that is severely affected in patients with schizophrenia (SCZ). Changes in dopamine receptor type 1 (D1R) function and availability in the PFC are associated with working memory deficits of SCZ. We previously showed that D1R constitutive activity increases voltage-gated calcium channels CaV2.2 density in the cell surface in transfected cells and that this effect is relevant in the PFC. Here, we continue to study D1/D5R constitutive activity modulation of native CaV currents and explore its impact on synaptic activity in PFC pyramidal neurons. We performed patch-clamp experiments and cAMP measurements on transfected HEK293T cells and wild-type C57BL/6 mouse brain slices, combining two pharmacological interventions to discriminate D1/D5R activity-dependent effects: systemic administration of chlorpromazine (CPZ, D1/D5R inverse agonist) and intra-PFC infusions of SCH23390 (D1/D5R antagonist). We assessed CaV subtype contributions to total native calcium current in naïve and treated mice. Then, we evaluated the impact of this pharmacological manipulation on synaptic activity: we recorded evoked, spontaneous and miniature excitatory/inhibitory postsynaptic currents (E/IPSC). We found that CPZ-treatment decreased EPSCs while increasing IPSCs, creating an E/I imbalance that favored inhibition. We are conducting experiments to further understand the link between D1/D5R constitutive activity and the changes seen in postsynaptic currents.

Etv4 regulates peripheral innervation and the development of peptidergic sensory neurons mediating pain stimuli.

Antonella Soledad Rios

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The perception of environmental stimuli in mammals is determined during embryonic development by specification of sensory neurons and peripheral innervation of the targets. Nerve growth factor (NGF) and its receptor TrkA are involved in many of these events and mediate pain sensation. The identification of molecules underlying NFG/TrkA signaling pathway is essential to understand the transduction of painful stimuli. Two members of the Pea3 subfamily of ETS transcription factors, Etv4 and Etv5, are known to be expressed by TrkA dorsal root ganglion (DRG) nociceptors and to be induced by NGF. Here we identify an essential role of Etv4 in target innervation and in the expression of the noxious-heat receptor TRPV1 in DRG neurons. Furthermore, we show that Etv4 deletion result in a reduced outgrowth of sensory neurons in response to NGF and in defects in growth cone architecture. Moreover, using different behavioral assays, we show that Pea3 deficient animals present defects in sensing thermal noxious stimuli. Together, our data reveal the relevance of Etv4 in regulating transcriptional programs involves in the transduction of pain signals.

Arylalkylamine N-acetyltransferase: “Nuclear importation and protective role against the blue light”

Maximiliano Rios

CIQUIBIC-FCQ-UNC

Arylalkylamine N-acetyltransferase (AANAT) is the key regulatory enzyme in melatonin synthesis present in the pineal gland, retina and other regions, controlled by light and the molecular clock. cAMP promotes its phosphorylation (pAANAT) triggering its activity. The vertebrate retina is a photosensitive tissue in which prolonged exposure to blue light (BL) may cause retinal damage and circadian clock disruption. Here we investigated the regulation of AANAT in primary cultures of chicken embryonic retinal cells exposed to different light conditions. AANAT expression is induced after 1h BL (1h post BL) as compared with dark (D) controls and displayed marked intracellular changes from the cytoplasm to nucleus increasing in BL and remaining elevated 1h post BL. Also, high pAANAT levels were detected in nuclear fractions of cultures after the BL treatment in comparison with D control. Knocking-down AANAT mRNA by specific shRNAs, cell viability assessed by MTT 24 h later was significantly affected by a 1h BL exposure as compared with the scramble, non-effects were observed in the dark conditions by MTT assay. In addition, ~50-60% of cells showed a significant decrease in levels of AANAT mRNA and -like protein. Results strongly suggest that AANAT is a BL-induced enzyme in retinal neuron cells, promoting its phosphorylation and nuclear localization, likely playing an important protective function in response to BL exposure.

Cocaine-base paste administration during adolescence alters the expression of genes involved in the excitatory/inhibitory balance in reward-system regions.

Lucia Santadino

Laboratorio de Neuroepigenética, Departamento de Química Biológica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires

Cocaine base paste (CBP) is a drug of abuse consumed mostly by adolescents and young adults in a socio-economically vulnerable situation in Latin American countries. We have previously studied the effects of CBP

on behavior using an open field test (OFT), resulting in an enhancement of anxiety-like behavior caused by CBP treatment. Considering that anxiety disorders are related to alterations of the excitatory/inhibitory balance, expression of genes involved in glutamatergic and GABAergic transmission was analyzed by real-time PCR in several reward-system regions. To do so, five-week-old CF-1 female mice were intraperitoneally injected daily with vehicle or CBP (40 mg/kg) for 10 day and subjected to a 10-day period of withdrawal. After that, medial prefrontal cortex (mPFC), nucleus accumbens (NAc) and amygdala (Amg) were isolated due to their implication in reward-seeking behavior. As a result, we observed a significant upregulation of Gria1, Gria2, Grin2b and Gad67 expression in the Amg of CBP-injected mice compared with the vehicle-injected group. Moreover, Gria1, Gria2, Gria3, Grin2b and Vglut presented a strong trend to increase whereas Vgat showed an opposite trend in the NAc of CBP group. Finally, the expression of Gria1 tended to increase in the mPFC of CBP mice. These results suggest that CBP administration during adolescence could lead to a disruption of the excitatory/inhibitory balance in the developing regions of the reward-system through gene expression changes

Synthesizing avian dreams

Juan Francisco Döppler

Laboratorio de Sistemas Dinámicos, Departamento de Física, FCEN, UBA; IFIBA-CONICET

Replays of behaviour-related neural activity during sleep have been shown to occur in different species, including rodents and oscine birds. In oscine birds, it has been shown that, while the pressure gesture needed to produce song is inhibited during sleep, these events of neural activity do arrive at the muscles of the syrinx (the avian vocal organ). These events of song-like muscle activity during sleep have also been observed in suboscine birds, which are usually considered non-learners. While in suboscines there is little knowledge about the neural structures related to song production, we here argue that biomechanics provides a unique window to study sleep replays. Firstly, because the signals arriving at the muscles represent the integrated output of the central nervous system. On the other hand, we have a more complete understanding of the physical mechanisms by which these instructions are translated by the muscles into specific properties (such as tension of the oscillating tissue), and therefore into sound. In this work we show how dynamical models of the biomechanics can be used to translate this activity into behaviour, to create biophysically plausible renditions of sound even when the patterns of activity are quantitatively different from those used during song production. In other words, we show how biophysical models can be applied to translate the EMG signals at the syringeal muscles into sound, to listen to what a bird is dream-singing.

Chemotherapy-induced changes in the expression of transient potential receptors in dorsal root ganglia and spinal cord of both male and female animals: implications for neuropathic pain generation

Constanza Miguel

Instituto de Biología y Medicina Traslacional

Chemotherapy-induced peripheral neuropathic pain (CIPNP) is a frequent and debilitating side effect of cancer therapy. Transient potential receptors (TRPs) are non-selective cation channels involved in the detection of thermal, chemical and mechanical stimuli and in the neurotransmission of pain. Their role in CIPNP has recently begun to be explored, as well as the existence of sex differences in pain behaviors in animals receiving chemotherapy. Here we evaluated the development of mechanical and cold allodynia in animals exposed to oxaliplatin, analyzing the existence of sex-related differences, as well as changes in the expression of TRPV1, TRPM8 and TRPA1 in the dorsal root ganglia (DRGs) and spinal cord (SC). Animals were injected with oxaliplatin, allodynia was evaluated using von Frey and Choi tests, and the mRNA levels of TRPs were evaluated by real time RT-PCR. Oxaliplatin administration induced the development of mechanical and cold hypersensitivity and allodynia in both male and female animals ($p<0.05$ vs control in both cases). No significant sex-related differences were observed. Oxaliplatin induced a significant increase in the expression of TRPV1 and TRPM8 in DRGs and SC from both male and female animals, while TRPA1 mRNA levels were increased only

in ganglia ($p<0.05$ vs control in all cases). Our results show that the upregulation of TRPV1, TRPM8 and TRPA1 might be involved in oxaliplatin-induced mechanical and cold allodynia in males and females.

Decoding of neural signals during the execution of motor skills in the mesencephalic locomotor region.

Jorge Mirande

Neurobiology of Movement Lab, Medical Physics Dept, Instituto Balseiro, UNCUYO-CNEA

The Mesencephalic locomotor region (MLR) is a shared structure among many species of the animal kingdom, from lampreys to human beings, classically known to contribute both to the generation and control of locomotion. Recent findings have highlighted the great functional and anatomical heterogeneity residing within MLR. While glutamatergic neurons in the dorsal MLR (cuneiform nucleus) are related to high-speed escape-like locomotion, in the ventral portion of MLR coexist different glutamatergic neuronal subpopulations involved in a range of behaviors beyond locomotion, such as rearing, grooming or handling. But, can this classificationq be taken even further? Can MLR neurons encode particular postures or movements? We have previously used unsupervised machine learning techniques to classify different types of recurrent movements executed by mice performing a motor skill learning task known as accelerating rotarod. In this work, we took advantage of the obtained movement classification to align the neuronal activity recorded extracellularly in MLR. By doing so, we were able to identified MLR neurons that are significantly modulated by specific postures or pose sequences. We then assessed whether neurons were recruited by other events such as a sudden fall of the tail base. Altogether, our data showed that MLR neurons are able to encode particular aspects of the executed movement.

YOUNG INVESTIGATORS TALKS

Minute-scale waves of activity in the medial entorhinal cortex

Soledad Gonzalo Cogno
Kavli Institute for Systems Neuroscience - NTNU

The medial entorhinal cortex (MEC) supports the brain's representation of space through the activity of multiple cell types, such as grid cells and head direction cells, whose firing is tuned to an animal's location and its movement through the environment. These cell types are embedded in the recurrently-connected MEC network and, as such, are expected to be coupled among themselves. How the structure of the MEC network, with its multiple co-existing cell types, constrains the spatiotemporal organization of neuronal activity and its population dynamics remains an open question. In this talk I will show that, during stereotyped locomotion and in the absence of sensory inputs tuned to navigation or external goals driving the animal's behaviour, neuronal activity in superficial layers of the MEC has the potential to self-organize into repeating sequences of neuronal activation. Such sequences, to which the large majority of the MEC recorded neurons are tuned to, propagate through the network at non-behavioural or plasticity-related timescales (tens of seconds to minutes), and do not exhibit any topography in their anatomical organization. The existence of this global, wave-like population dynamics has the potential to couple distinct and anatomically distant functional cell types.

Hippocampal-Prefrontal cortex connectivity in theta band during memoryrecall is modulated by the contextual novelty of an item

Juan Facundo Morici
Girardeau Lab: Sleep and Emotional Memory, Institut du Fer à Moulin, INSERM U1270, Sorbonne Université, Paris, France
1) Instituto de Neurociencias Cognitiva y Traslacional, Concejo Nacional de Investigaciones Científicas y tecnológicas (CONICET), Universidad Favaloro, Instituto de Neurología Cognitiva (INECO), Buenos Aires, Argentina.
2) Instituto de Fisiología y Biofísica "Bernardo Houssay" (IFIBIO-Houssay), Grupo de Neurociencia de Sistemas, Universidad de Buenos Aires, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) Buenos Aires, Argentina.

Remembering which experiences occurred in a particular context is a complex process that requires the interaction between multiple brain areas. The recall of a specific memory can be triggered by contextual information and relies on the interaction between the hippocampus (HPC) and the prefrontal cortex (PFC). It has been shown that the synchronization of HPC-PFC theta oscillations is enhanced during the resolution of contextual/spatial working memory tasks. However, little is known about how the HPC and PFC are coordinated during a contextual-guided recall of episodic-like memory. To address this, we performed electrophysiological recordings in rats during the retrieval phase of the object-in-context memory task. Animals had to learn two different object-context associations. During the Retrieval phase, animals were reintroduced to one of the contexts with one copy of each object presented before. In this setting, both objects are known by the animal. However, one of them is presented in a contextual mismatch. We observed an increase in the LFP coherence and amplitude coordination between the ventral HPC (vHPC) and PFC in the theta band when animals explore the contextually mismatched object. Also, the level of differentiation between these two conditions predicts the performance of the animals in the task. These results suggest that HPC-PFC functional connectivity in the theta band is differentially modulated depending on the contextual congruence of the presented stimuli.

Gisela Zalcman
Laboratory of Physiology and Algorithms of the Brain

Spatiotemporal reorganization of corticostriatal network dynamics encodes motor skill learning

Motor skill learning is an adaptive process in which a complex motor command is learned and stored, sometimes for a lifetime. This learning is characterized by an early phase, dependent on the dorsomedial striatum (DMS) and in which the basic motor coordination is acquired. And a late phase, dependent on the dorsolateral striatum (DLS) in which subsequent practice leads to automatization of the behaviour. Here, we studied which specific neuronal ensembles encode both phases of motor skill learning. Using ex vivo two-photon calcium imaging, we found a spatiotemporal reorganization of corticostriatal networks dynamics with the formation of activity patterns specific to each territory at both stages of learning. During the early phase, the overall activity of DMS decreased, with few and sparsely distributed highly active (HA) cells remaining. In contrast, the DLS showed a long- lasting formation of clusters of HA cells. These two sequential phases of network reorganization arised from a reinforcement of synaptic connections from cingulate cortex onto DMS HA cells and long-lasting anatomical rearrangements of somatosensory projections to the DLS. Using an AAV cFos-TRAP strategy combined with chemogenetics, we further demonstrate that silencing of HA cells in DMS or DLS strongly impairs the individual performance. Therefore, discrete domains of highly active neuronal substrates sequentially encode early acquisition in DMS and long-lasting retention of motor skill learning in DLS.

José Duhart
Department of Neuroscience, Farber Institute for Neurosciences, Thomas Jefferson University, United States.

Nutrition tilts the balance between sleep and reproduction in Drosophila

Sleep is incompatible with other behaviors, and therefore animals must choose between accomplishing different tasks or fulfilling the need for sleep. Environmental cues and internal states are integrated to make proper behavioral choices under varying conditions. In this work, we explored how access to food of differing qualities affects the decision between sleeping and performing reproductive behaviors in Drosophila. While well-fed male flies paired with female partners reduced sleep to engage in courtship, protein-deprived males showed attenuated female-induced nighttime sleep loss. Similarly, female flies showed a marked reduction in nighttime sleep after mating, but only when they had access to a food substrate adequate for egg-laying. We next identified several components of the neural circuits relevant for computing these behavioral choices. We found sleep-suppressing protocerebral bridge-projecting neurons that, together with the male-specific P1 cluster, build a male-specific sleep regulatory circuit that can be modulated by protein availability. In addition, female-specific pC1 neurons were necessary for nighttime sleep loss in mated females, and both olfactory and gustatory sensory circuits contributed inputs about food quality to modulate female post-mating sleep loss. Our work provides novel insights into how organisms weigh conflicting motivations to select the appropriate behavior under different contexts.

Malena Lis Mul Fedele
Chronophisiology Lab, Institute for Biomedical Research (UCA-CONICET), Buenos Aires, Argentina.

Sleep and circadian characteristics related to incidents reported by medical residents

During medical training, residents experience sleep and circadian disorders due to extended work hours and shift work. These alterations lead to a reduction in mental and physical performance capability which can affect resident's safety and well-being, and have potentially adverse implications on patient care (Basner M 2017). The aim of the present study was to explore the presence of sleep and circadian alterations in Argentinian medical residents and its relationship with incidents that happened to the professional at the hospital. We

analysed these variables subjectively in a group of 661 medical residents, and we carried on an objective study in a group of 37 of them. The group that informed incidents, reported sleeping less per working day and we found that sleep debt was about 30 minutes greater than the ones who reported not having incidents. This group also reported higher scores of anxiety, depression and burn out. Regarding the objective measures, we found that residents that reported incidents worked more hours of extended shift and that they slept more hours during the day and less hours during the night than those who didn't. Finally, we also studied the temperature rhythm and found that those who reported incidents had a lower amplitude and percentage of rhythmicity than those who didn't, suggesting circadian misalignment. These results suggest the development of new methods to monitor circadian misalignment, to prevent incidents in health care facilities.

Yanel Andrea Volonté
Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB), Universidad Nacional del Sur (UNS)

Neuroendocrine control of an innate behavior

Knowing how neural circuits integrate information from multiple sources to generate a response is essential to understand the fundamental principles of animal behavior. During development, flies, as other animals, show drastic changes in their neuromotor behavior program. At the end of the larval period, the long, flexible and transparent cuticle of D. melanogaster larvae is transformed into a short, sclerotized and tanned puparium. This remodeling is achieved by a series of muscular contractions and structural modifications of the cuticle, both of which are not completely understood at the molecular level. It was previously shown that the Dilp8-Lgr3 pathway are part of a neuroendocrine circuit that promote developmental stability by delaying a peak of Ecdyson that commits larvae to initiate metamorphosis. Here, we describe how the Dilp8-Lgr3 pathway acts to promote the progression of the pupariation motor program. During this process, Lgr3 is required in a set of neurons of the CNS, different than those related to developmental stability, to transduce the Dilp8 signaling that is triggered as a response to Ecdysone in the cuticle epidermis. Our work suggests that Dilp8-Lgr3 constitute a new neuroendocrine pathway directly contributing to puparium morphogenesis; and serves as a model for understanding neuro-hormonal circuits that control complex behaviors.

Maria Mercedes Benedetto
INIMEC- CONICET- UNC

Retinal degeneration promoted by constan low light exposure

The vertebrate retina is the neural portion of the eye responsible for transducing light in a pattern of electrical impulses to the brain. In mammals, light acts directly in retina to fulfill the visual function through rods and cones, and the non-image forming tasks, carried out by intrinsically photosensitive retinal ganglion cells (RGCs). Retinal Degeneration (RD) is any pathological process that causes the death of retinal cells inducing the loss of its structure or function. Light is an important factor which produces or accelerates RD. Due to this, light induced RD is used as a model to study human RD that arise by environmental injuries, aging or genetic disorders. We are interesting to study LED sources since they emit blue light, which has been shown to have a powerful role on RD process. So, we aimed to study the biochemical mechanism of RD, in a murine model of RD by constant exposure to low intensity LED light. Our results show that belong the days of light exposure there is deep retinal remodeling, affecting its functionality, rhodopsin phosphorylation, photoreceptors cell deaht and redox imbalance; correlated with a variation in photoreceptors fatty acid composition. Besides, the survival of RGCs is not affected; however, there are changes in the distribution and expression of some non-visual opsins. Overall, the results allow us to consider this model as a useful tool to elucidate the events of RD triggered by constant exposure to low intensity LED lights.

Natalia Andrea Marchese

CIQUIBIC-CONICET- Departamento de Química Biológica Ranwel Caputto- Facultad de Ciencias Químicas, Universidad Nacional de Córdoba

Müller glial cells as novel photosensitive components in the vertebrate inner retina

Located all along the inner retina, Müller glial cells(MC) take part in development, metabolism, neurotransmission, injury response and regeneration. Non-canonical opsins in the retina sense environmental lighting conditions along the day to drive specific non-image forming functions(NIF), that include the entrainment of circadian rhythms. Our recent studies in the understanding of NIF in the avian inner retina are focused on light-driven responses of MC. Initially, we identified a gradual increase, throughout development up to the time of hatching, in the expression of Opn3 and glial markers. Furthermore, MC in culture show photic-regulated expression and location of Opn3. Moreover, we identified a direct photic response of MC to a blue light(BL) pulse as an increase in intracellular Ca2+ levels. This response is sustained for several minutes, dependent on opsin activation, specific to BL stimulation and comprises three subpopulations: A. ≥20% increase; B. 10-20% increase; and C. No-increase. MC activation involves Ca2+ release from endoplasmic reticulum(ER); as their depletion decreased the percentage of MC effectively responding to BL, whereas an extracellular Ca2+ chelator did not. Indeed, cytosolic Ca2+ increase goes along with a decrease in Ca2+ levels in the ER. MC can be postulated as new intrinsically photosensitive components in the inner retina of vertebrates potentially contributing to local circuits in the regulation of various physiological processes by BL

Paula Andrea Soto

Instituto de Química y Fisicoquímica Biológica "Alejandro Paladini" UBA-CONICET, Facultad de Farmacia y Bioquímica.

Combining strategies to promote peripheral nerve regeneration.

Peripheral traumatic injuries constitute a problem of public health with high prevalence worldwide and the development of new treatments is of great importance. Cell therapies have provided encouraging outcomes, but a major obstacle is to secure enough cells at the injured site to warrant therapeutic effects. To tackle this issue, we proposed a strategy combining adipose derived mesenchymal stem cells (AdMSC) loaded with superparamagnetic nanoparticles (SPIONs) and their mobility enhanced by the application of an external magnetic field gradient (magnetic targeting, MT). The aim of the present work was to test whether MT can help AdMSC-SPIONs reach specific tissue and thus improve the regenerative ability of AdMSC upon sciatic nerve lesion. To this end, AdMSC, SPIONs, and SPIONs internalized by AdMSC were extensively characterized and AdMSC-SPIONs arrival and retention at the injured nerve were evaluated. Finally, cell transplantation effects on regeneration were assessed both in terms of nerve morphology and impulse conduction. AdMSC arrival to the injured nerve was significantly increased using MT and their beneficial effects surpassed the regenerative properties of the stand-alone cell therapy. AdMSC-SPIONs group showed remarkable restoration in myelin basic protein organization, resulting in an improvement in nerve conduction values. Our results prove that MT of AdMSC-SPIONS constitutes a valuable tool to promote nerve regeneration.

Bruno Gabriel Berardino

Laboratorio de Neuroepigenética y Adversidades Tempranas, Departamento de Química Biológica - IQUIBICEN (CONICET), Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires

A multifactorial murine model of social and material deprivation: molecular mechanisms underlying aggressiveness

Early-life adversities (ELA), such as child low socioeconomic conditions, affect the structure and function of the brain leading to impaired health and psychological well-being later in life. With the aim of understanding the

neurobiological sequelae and mechanisms of risk of ELA, we designed and validated a multifactorial murine model of social and material deprivation (SMD) produced by a set of adverse environmental factors. Dams exposed to SMD offered less care to their pups than control dams and displayed depression-like traits. Regarding offspring, SMD treated mice presented dominant behavior, and SMD males showed signs of aggressiveness. Since prefrontal excitatory/inhibitory balance (E/I balance) may account for behavioral alterations, particularly aggressiveness, produced by ELA reprogramming during development, we analyzed the expression of genes involved in E/I balance in the mPFC. We found an increase in Grin1, Grin2B and Grin2A expression in SMD females and a slight increase in Grin2B in SMD males for NMDA-related genes; and no changes in AMPA-related genes. Serotonin system has also been involved in aggressive behavior. We found an increased expression of prefrontal 5ht1A in SMD male mice, but not females. These results sustain the face validity for the proposed SMD model, which allows us to continue approaching its target validity. Gene expression alterations in the mPFC provide a molecular mechanism for understanding the neurobiology of exposure to adverse socioeconomic conditions.

Constanza Garcia Keller
Medical University of South Carolina, SC, USA

Glutamatergic Mechanisms Mediate Enduring Vulnerability to Drug Use Following an Acute Stressor

Epidemiological studies indicate that acute life threatening events increases the incidence of post-traumatic stress disorder (PTSD), and a diagnosis for PTSD carries 30-50% comorbidity with substance use disorder (SUD). Presentation of drug-associated cues evoke transient potentiation (t-SP) in the tetrapartite synapse, including pre and postsynaptic neurons, astrocytes and the extracellular matrix (ECM). Given the overlap between the enduring adaptations produced by stress and drug use, I hypothesize that exposure to a stress-conditioned stimulus (stress-CS) elicits t-SP and coping responses in defensive burying (DB). Moreover, MSNs constitute 90-95% of the neurons in the NA and are chemically coded into D1 or D2 dopamine receptors. Generally, D1-MSN activation promotes behavior, and D2 activation inhibits behavior. Thus, I also hypothesize that stress cue-induced t-SP will occur in D1-MSN. I observed that stress-CS exposure is associated with synaptic potentiation in NAcore quantified as: increased spine head diameter and density, increased metalloprotease-9 activity that catalyzes proteins from the ECM, and astrocyte retraction from synapsis compared to control animals. Then, doing single cell Ca2+ dynamics in D1- and D2-MSN of freely moving mice and cre-dependent Ca2+ indicator, I observed differential changes in Ca2+ activity of D1 vs D2-MSN during stress and DB. These changes seem to be correlated with t-SP and lead to stress coping responses.

Alejandro Villarreal
Laboratorio de Neuropatología Molecular, Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis" UBA-CONICET, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

Chromatin remodeling as an underlying epigenetic mechanism of astrocyte neuroinflammatory phenotype stability

Astrocytes respond to brain injury through a phenomenon called "reactive astrogliosis", in which a pro-inflammatory and pathological phenotype has been described, thus representing a promising target to reduce damage propagation after injury. Astrocyte pro-inflammatory gain of function involves stable transcriptomic changes probably following transcription factor NF-kB activation. We hypothesized that astrocyte pro-inflammatory phenotype is sustained by NF-kB-associated epigenetic mechanisms that regulate gene expression. Using mouse primary glial cultures we observed that the pro-inflammatory stimulus LPS (Lipopolysaccharide) promotes NF-kB activation first in microglia and then in astrocytes where it remained active for 72hs. The strength of initial activation in astrocytes depended on microglia abundance and the release of microglial soluble factors. We further observed a microglial-dependent increase in gene activating histone marks H3K9K14ac and H3K27ac and a decrease in the repressive mark H3K9me3. In vivo, H3K27ac increased specifically in reactive astrocytes in a model of brain ischemia by cortical devascularization in rats. The observed changes in histone modification abundance dynamically occurred in pro-inflammatory astrocytes

suggesting events of chromatin remodeling. Such mechanisms may represent plausible targets to reduce astrocyte pro-inflammatory phenotype, neuroinflammation and neuronal loss after brain injury. Grants: UBACYT, FONCYT, ISN-CAEN, APBIOTECH

Julieta Aprea
Center for Regenerative Therapies Dresden

The lncRNA B13 regulates the NSC fate choice between proliferation and differentiation.

During cortical development, neural stem cells (NSCs) have to either proliferate to expand the progenitor pool or to differentiate to give rise to more committed cells. This NSC fate choice between proliferation and differentiation is critical to determine the correct number and identity of the neuronal and glial output. However, the molecular mechanism regulating this choice is not completely understood yet. I have identified B13 as a novel gene involved in neural commitment of NSCs in the developing cerebral cortex, where its transcript is characteristically up-regulated in progenitors committed to differentiate. The nature of this gene was originally not clear, as it had been annotated in some databases as a long non-coding RNA (lncRNA) and in others, as a protein. Through a series of experiments to distinguish between these two possibilities, including the generation of four antibodies against the protein potentially encoded by B13's longest open reading frame, I show that B13 is a lncRNA. Furthermore, using gain of function experiments in vivo, I show that B13 has a cell intrinsic role, inducing the proliferation of committed progenitors at the expense of differentiation; and a cell extrinsic effect, increasing the overall number of progenitors in the developing cortex. This increase in the progenitor population leads later in development to a larger neuronal output. This lncRNA will allow us to understand the role played by lncRNAs in the expansion of the cerebral corte

Daniela Di Bella
Department of Stem Cells and Regenerative Biology, Harvard University

Multi Modal Atlas of Cellular Diversification in the Mouse Cerebral Cortex

The mammalian cerebral cortex contains an unparalleled diversity of cell types, which are generated during development through a sequence of temporally orchestrated events that are under tight evolutionary constraint and are critical for proper cortical assembly and function. However, the molecular logic that governs the establishment and topographic organization of cortical cell types remains elusive. This is largely due to the need for investigation of a vast numbers of cell types through dynamic cell-state transitions, and over developmental time. We have generated near-saturation, single-cell RNA-seq and single-cell ATAC-seq datasets of the developing mouse neocortex, sampled every day through the duration of embryonic corticogenesis and complemented with a spatial transcriptomics time-course. At this coverage, we were able to identify the full array of known cortical cell types and computationally reconstruct developmental trajectories across the diversity of cortical cell classes, linking progenitors to their full spectra of neuronal and glial progeny. From this we infer their spatial organization and unveil gene regulatory programs that accompany their fate specification and diversification. The data provides a global picture of the regulatory mechanisms governing cellular diversification in the neocortex.

Ivan Mestres
Center for Regenerative Therapies (CRTD) / Uniklinikum Dresden

SLAPping the brain. How a nuclear envelope protein makes you more cautious

Can you believe there still are genes whose functions are totally unknown? In this talk, I will share with you my first hints on the role of SLAP, a nuclear membrane protein specifically expressed in the brain. When manipulated during development, SLAP shifted the fate of neural progenitors affecting the layering of the brain cortex. All of which triggered changes in the exploratory behavior of postnatal mice.

Active search signatures in a free-viewing task exploiting concurrent EEG and eye movements recordings

María da Fonseca

Laboratorio de Inteligencia Artificial Aplicada, Departamento de Computación, Facultad de Cs Exactas y Naturales, UBA

Visual search involves a series of mental processes that guide the eye movements through the visual scene. Early access to categorical visual information plays an important role during free-viewing. In fixed-gaze, there are well-established electrophysiological signatures of categorical processing. For instance, a hallmark of face processing emerges around 170 ms after stimulus onset with an increased EEG amplitude to faces. Here, we aimed to study how the sensitivity to category information extends to a free viewing paradigm. We co-registered brain activity and eye-tracking to investigate fixation-related potentials to pictures of different categories during visual search and exploration. We hypothesized a larger evoked response to face fixations in comparison to objects. Besides, we proposed that the brain signatures reflect a different behaviour underlying the active search for a target during the visual search task in comparison to the mere exploration of items during the exploration task. In this study, we show a stronger activation for fixations to faces than to objects in both types of tasks. With a deconvolution analysis/approach of the EEG signal, we found significant early differences between the components elicited by fixations to pre-target stimuli and exploration stimuli. These results generalize the characterization of early visual face processing to a wider range of experiments and show specific components potentially associated with eye movement guidance.

E-SOCIALS

Navigating the gray areas to do Neuroscience

The transition from postdoc to establishing and running your own lab is a crucial step in academia. This process, which is critical everywhere in the world, presents additional difficulties in our country. Which are the main challenges we face to academic independence? Is it easier to settle and do neuroscience abroad? What does it mean to return to the country through repatriation? How to achieve a balance between family and work roles? How to access grants and/or international collaboration networks?. These are just some of the questions and doubts that emerge at the moment of starting an independent career. In this roundtable, early- career scientists who are at this critical stage, together with established researchers who have already gone through it will share their experiences and discuss with the audience the challenges, pitfalls and different opportunities that exist in our country for junior PIs.

Lista de oradores que cuentan su experiencia personal en 5 min y luego se abre a preguntas del público:
Diego Rayes y Graciela Mazzone (moderadores)

- **M. Valeria Canto-Soler, PhD**
  Doni Solich Family Chair in Ocular Stem Cell Research. Director of CellSight – Ocular Stem Cell and Regeneration Program. Associate Professor – Department of Ophthalmology. University of Colorado School of Medicine
- **M. Florencia Coronel** , PhD.
  Investigadora Adjunta – CONICET. Laboratorio de Dolor en Cáncer. Instituto de Investigaciones en Medicina Traslacional. CONICET – Universidad Austral
- **M. Soledad Esposito** , PhD
  Investigadora Adjunta – CONICET. Laboratorio de Neurobiología del movimiento. Departamento de Física Médica, Gerencia de Física, Centro Atómico Bariloche, Argentina.
- **Tomás Falzone**
  Investigador Independiente (CONICET), Jefe de Trabajos Prácticos, DS 1ª U. A. Depto. Histología, Biol. Cel. y Genética. Facultad de Medicina, UBA.
- **Emilio Kropff, PhD**
  Investigador Adjunto- CONICET. Physiology and Algorithms of the Brain. Leloir Institute – FIL – IIBBA/ CONICET
- **Nara Muraro,** PhD
  Investigadora Adjunta CONICET. Neurobiología del Sueño. IBioBA – CONICET – MPSP, Instituto de Investigación en Biomedicina de Buenos Aires – Instituto Partner de la Sociedad Max Planck
- **Gabriela Salvador, PhD**
  Investigadora Independiente de CONICET. Profesora Adjunta Universidad Nacional del Sur. Metaloneurobiología y señalización celular. Instituto de Investigaciones Bioquímicas de Bahía Blanca (INIBIBB)- CONICET -Bahía Blanca
- **Nicolás Unsain , PhD**
  Investigador Adjunto- CONICET. Instituto de Investigación Médica Mercedes y Martín Ferreyra - INIMEC/ CONICET – Universidad Nacional de Córdoba.

Socio-environmental modulation of cognitive processes

Cognitive processes occur in particular socio-environmental contexts that can modulate their development and/or performance. This table will address this complexity through the dialogue between the 4 papers to be presented, which will analyse the emotional and cognitive development of preschoolers in their contexts, the causal connectivity of statements beyond the learning process and discourse comprehension of information acquired from Comprehensive Sex Education (CSE) materials, how the physical variables of schools contribute to the perception of children, and how political decisions (voting) can be induced by the parameters of campaigns and dissemination of content. **Presentations (and speakers):**

Influence of individual and socio-environmental factors in a task with positive emotional valence and demand for inhibitory control and cognitive flexibility Ramírez, Verónica Adriana*a,b; Ruetti, Eliana a,b *a Unidad de Neurobiología Aplicada (UNA, CEMIC-CONICET), Ciudad Autónoma de Buenos Aires, Argentina b Facultad de Psicología, Universidad de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina* There is a large literature on the interdependence of cognitive and emotional processes, and their modulation through individual and socio-environmental factors. Preferential processing of emotional stimuli over neutral ones has been evidenced, which has been widely studied in inhibitory control paradigms, such as the Stroop task, due to its simplicity and ease of incorporating emotional valence. Unfavorable early experiences are associated with low levels of performance in tasks with demands for inhibitory control. The present research analyzes the role of socio-environmental factors in emotional processing, inhibitory control, and cognitive flexibility in children between 4 and 8 years old. A Stroop-type task with positive emotional valence was administered and its association with socio-environmental variables was studied, such as the level of stimulation at home and the type of work and schooling of mothers/fathers. An environment with greater stimulation positively influences task performance but without affecting reaction time. Furthermore, this relationship varies depending on the gender and age of the participants. These findings indicate that individual and contextual variables are closely associated with performance in a task of inhibitory control and cognitive flexibility and that they need to be analyzed together to provide a better understanding of their influences throughout child development. Keywords: emotional stroop, emotional processing, home stimulation, individual and socio-environmental factors.

The Role of Causal Connectivity, Note-taking and Modality of Presentation in the Comprehension of Materials about CSE (Comprehensive Sex Education) *Karen Acosta Burallia & Jazmín Cevascoa,b* a University of Buenos Aires b National Scientific and Technical Research Council (Argentina) The goal of this study was to examine the role of the causal connectivity of the statements (Low-Medium-High) and the condition of note-taking (focused on speakers' emotions, focused on the comprehender's emotions or focused on the importance of the topic of the materials). With this aim, we asked a group of college students to read or listen to an excerpt of an interview with highschool students and teachers about CSE, and to answer to an elaboration question (Considering the materials that you read/listened to, how would you define CSE?). Results indicated that statements that had a high number of causal connections were more included in the notes participants took and their answers to the elaboration question, and that causal connectivity had a greater effect when participants listened to the materials, and when they took notes focused on the importance of the topic. Also, listening to the interview and taking notes focused on the importance of its topic promoted that students included a higher number of statements in their notes than reading its transcript. These results highlight the importance of promoting that students take notes, listen to the materials and establishing a high number of discourse connections during discourse comprehension. Key words: Comprehensive Sex Education – Discourse Comprehension – Note-Taking – Causal Connectivity

Complex decision-making is facilitated by social modulation Bernal, Franco Agustín a ; Alves Salgueiro, Tomás a; Brzostowski, Axel b; Caramés, María Ayelén a; Recart Zapata, Emilio a; Furman, Damian b,c; Pérez, Juan Manuel b,c; Fernandez Larrosa, Pablo Nicolas a. a. Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE), UBA-CONICET b. Departamento de Computación, UBA c. Instituto de Ciencias de la Computación (ICC) UBA Some decision-making (DM) processes require quick answers, while more complex decisions demand greater cognitive engagement. Under the hypothesis that frequent exposure to a stimulus or association with an emotional valence could drive DM, online experiments were conducted and results were compared with a more "ecological" situation (Social Study) involving: 1. online surveys conducted during the 2019 Argentine Presidential Elections; 2. a dataset of written media news to assess each candidate's mention frequency and sentimental analysis. Cognitive experiments involved a computer task where participants choose a face from 4 options, each of them associated with different frequencies (EXP#1) or with positive, negative, neutral, or mixed sentences (EXP#2). Two experimental groups were set up: the 1st was asked to choose a face without any specification (NST); and the second group was asked to choose a person to perform an important task (IT). Results show: 1. The most repeated face was significantly more chosen in the NST group, involving significantly greater response time; 2. The faces with a positive association were significantly more chosen than others, in both groups; and 3. The effect persisted at least for 24hs. The social study supported our experimental results as Familiarity (F) and Trust (T) mostly explain the Voting Probability (VP), as well as F, T, and VP for each candidate correlate significantly with the frequency of mentions, the positive association, and election results. These results support our hypothesis and suggest that complex decision-making susceptibility to social modulation could depend on the relevance of the involved task. Keywords: Complex Decision-Making; Priming; Presidential Elections.

LEARNING, SPACE, EMOTION. The relationship among the 7 environmental variables and the learning of new languages. Case Study: CIL Language School, in Cordoba, Argentina Vanina Salinas, Gisele Rocha Maggi, Mayara Wal, Danielli Wal e Bruna Probst Group of Study of Neuroscience applied to Architecture from Curitiba/PR – Brazil The Coronavirus has had a strong impact in education. Neuroscience studies indicate that the environment influences the learning process because the individual has an innate ability to capture what surrounds him or her. This article tries to identify seven environmental variables: colors, smells, shapes, sounds, biophilia, functionality and lighting, verifying how students in the age from 7 to 15 years can perceive the school physical space. Starting from a bibliographic review, we base our study on the case of CIL, a language school in Córdoba, Argentina, which has its own teaching method incorporating the use of positive emotions through the free use of space. This relationship between learning, emotions and space will be observed through the adapted use of the EAPA tool (Self-Perception of Environments Scale), applied through a questionnaire answered by 20 students who attended face-to-face classes during 2019 and in 2021. From the results to be obtained, we hypothesize that an appropriate school environment stimulates cognitive development and provides better learning outcomes. From the results of EAPA, the environmental variables that directly impact the learning process will be identified and will determine which variables could be applied according to the reality of schools around the world. Therefore, this tends to contribute and promote improvements in the learning and teaching process as well as in the advancement of existing methodologies, resulting in a better quality of learning and an improved perception of the environments. Key Words: school architecture, Language schools, Environmental variables, Escala de autopercepción de los ambientes (EAPA), Perception of the student's environmental variables, ANFA 2021

Co-authorship network structure and gender inequalities of the Argentine neuroscientific community

Gender inequalities in academia exist in a wide variety of fields and circumstances. Owing to the particularities of the Argentine scientific system, gathering appropriate data for the national neuroscientific community poses a challenge thus making it difficult to compare our situation with the one in Neuroscience as a field in a global sense. We want to show local generated data or neuroscience in Argentina and understand it in a global context. First, Dr. Calero will introduce the subject of gender inequalities in the academic world globally, including differences in salaries, hierarchies, funding and lead authorships. Second, Dr. Bekinschtein and Lic. Ramos Usaj will discuss novel analyzed data that show the evolution and current state of the network structure in the local neuroscientific community and provide a launching platform for an open public dataset created from published reports from the Annual Meeting of the Sociedad Argentina de Investigación en Neurociencias and public government data from the Science and Technology staff, to serve as a call to action to all national neuroscientists.

Despite several changes throughout the years, the abstract books from the Annual Meeting of the Sociedad Argentina de Investigación en Neurociencias (SAN) collect information regarding poster submissions among other things and, in particular these books contain the poster title, topic, authors, affiliations and the poster abstract. We parsed poster data from the digital versions (.pdf files) of the abstract books of the SAN Annual Meetings from the year 2012 to the year 2019 (with the exception of the year 2016) to recover valuable poster information, mainly the poster title, authors, topic and abstract. Since the 2020 SAN Annual Meeting was entirely virtual we scraped data from the 2020 Annual Meeting website to gather the same poster data as before.

We also accessed public data from the SICYTAR (Sistema de Información de Ciencia y Tecnología Argentino) to gather the name, self-reported sex and other information about all people who are related to R+D activities that conform the national science and technology staff. We performed name matching and established record linkage between the extracted poster data and the SICYTAR data using the distance score from a K Nearest Neighbour (KNN) algorithm. As a follow-up metric we used fuzzy string matching algorithms between the target poster author name and the closest match (following the KNN algorithm) from the SICYTAR data. All the data gathered plus the methods used to extract and transform it are made publicly available in a GitHub repository. Using an extremely conservative threshold for the KNN algorithm score we constructed a co-authorship network from the poster authors and took a glance at the basic graph features (size, density, components, diameter, clustering coefficient and network centrality) over time. Furthermore, we focused on a small aspect of the dataset to assess gender inequalities by examining the men-women proportion in the meeting attendants and the sex-specific distribution of author positions using both frequentist and bayesian approaches.

Speakers

Cecilia Calero
Investigadora Adjunta – CONICET. Laboratorio de Neurociencia. Universidad Torcuato Di Tella

Pedro Bekinschtein
Investigador Independiente – CONICET. Instituto de Neurociencia Cognitiva y Traslacional – INCYT CONICET – Fundacion INECO – Universidad Favaloro

Alejandro Ramos Usaj
Doctorando. Instituto de Cálculo. Universidad de Buenos Aires

Looking for training abroad? Tips for international interviews

How to start the search for a research stay or a PostDoc abroad? When we start our PhD we wonder how to do a research internship in a laboratory abroad. Furthermore, by the end of the PhD we find difficulties searching for PostDocs opportunities. The key is to build collaborative networks and a plan! In this session we will discuss: How to find a laboratory according to our topic of interest and the available scholarships? How to finance the trip? How are the interviews with the principal investigators? Are these face-to-face or virtual? How are interviews organized? How should we prepare? Do you have to give a presentation? Is the presentation only with the director or is the rest of the team present? How many interviews people usually do until getting a stay or PostDoc? We will also talk about looking for opportunities for scholarships and courses during the PhD and alternative for financing the attendance to conferences abroad?

we will have asynchronous interventions (on video) by foreign researchers who will tell us what they look for in interviews when they are recruiting PostDocs. We will also have argentinean PostDocs that will tell us about their personal experience. Afterwards, we will continue with questions and an open conversation.

Would you join us?

Moderadores:
Javier de Zorrilla San Martín, Macarena Fernández y Esteban Beckwith

Investigadores extranjeros

Ian Forsythe
Emeritus Professor of Neurophysiology. Department, Neuroscience, Psychology & Behaviour (NPB).College of Life Sciences, University of Leicester

Giorgio Gilestro
Senior Lecturer. Faculty of Natural Sciences, Department of Life Sciences. Imperial College London. United Kingdom

PostDocs/ Investigadores asistentes
Ivana Bussi
Ivana Bussi, PhD. Becaria posdoctoral CONICET. Laboratorio de Genética del Comportamiento. Fundación Instituto Leloir

Mariano Polo
Mariano Polo, PhD. Investigador Asistente CONICET. IHEM-CONICET, Facultad de Ciencias Médicas. Universidad Nacional de Cuyo

Evelin Cotella
Evelin Cotella, PhD. Postdoctoral Research Associate. Cancer and Hematology Division. Cincinnati Children's Hospital Center

Diego Fernández
Diego Fernández, PhD. Associate scientist at the Section of Light and Circadian Rhythms. National Institute of Mental Health (NIMH/ NIH), USA.

Scientific Publications: Journals and Editorial Policies

Getting a scientific manuscript published is usually challenging. Several doubts usually appear before submitting a paper. Which is the most appropriate journal for my paper? What is each of the steps in the paper review process? What do journals look for in terms of the acceptability of a manuscript? There are a growing number of journals that scientists can consider when making decisions about their papers. Each journal has a content, protocol, and peer review process that are quite unique to its publication missions. In this session, we will explore the nuts and bolts with:
Dr. Ian Forstyhe (Former Editor-in-Chief at the Journal of Physiology)
Dr. Eve Marder, (Former Deputy Editor at eLife)
Dr. Shari Wiseman, (Chief Editor at Nature Neuroscience)

Specifically, our guests will cover:

* Historical perspective context in which these journals were established and their current role

*What their journals look for in research submissions

*Considerations and nuances of writing for their publications

*The peer-review process

There will be a Q&A and discussion section for the audience to interact directly with our panelists about this critical aspect of a career in science.

Gender inequities and inequalities around the world

Women comprise a minority in Science, Technology, Engineering, Mathematics, and Medicine (STEMM) workforce. STEMM gender inequalities can be revealed in different and specific forms depending on sociocultural aspects of certain research areas and/or country analyzed. For this third edition, we´ll receive eight outstanding women scientists from different disciplines around the world, who share a strong advocacy for gender issues in science. We are happy to continue with this new tradition established in SAN annual meetings where we can dedicate time to discuss where we stand in the gender gap, and how we can move forward in closing it.

Dr. Shohini Ghose, Professor of Physics and Computer Science and NSERC Chair for Women in Science and Engineering; Director, Centre for Women in Science, Wilfrid Laurier University, Canada.

Dr. Shazrene Mohamed, Associate Professor, South African Astronomical Observatory, Cape Town, South Africa.

Dr. Shobhana Narasimhan, Professor of Theoretical Sciences, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India.

Dr. Silvina Ponce Dawson, Principal Investigator in CONICET, Full Professor Physics Department, Biological Physics and Photophysiology Group, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina.

Dr. Rabia Salihu Said, Full Professor of Atmospheric Physics, Department of Physics, Bayero University, Kano, Nigeria.

Dr. Ana Silva, Full Professor, Neuroscience Lab, Facultad de Ciencias, Universidad de la República de Uruguay, Uruguay.

Dr. Marie-Francoise Roy, Emeritus Professor, Effective Geometry and Algebra Group, Institut de recherche mathématique de Rennes, France.

Dr. Cecilia Bouzat. Full Professor, Universidad Nacional del Sur. Instituto de Investigaciones Bioquímicas de Bahía Blanca. Buenos Aires, Argentina.

NeuroCine

El Hijo de la Novia: 20 años no es nada.
Diálogo entre la ciencia y el cine.
(this activity is full in spanish)

Chairs: Juan Ferrario & Elena Avale

En 2021 se conmemoran 20 años del estreno del "Hijo de la Novia", una de las películas Argentinas que quedó en la filmoteca de lujo del cine nacional, incluída en el selecto club de películas locales nominadas a los premios Oscar y cuya rica trama incluye centralmente la Enfermedad de Alzheimer.

¿Cómo se presenta un tema científico/médico dentro de un film ?
¿Cómo es el *backstage* de la rigurosidad de comunicación de la ciencia ?
Desde el cine, ¿se lo piensa como una herramienta de divulgación ?
La ciencia (positivista y en su versión "ciencia ficción") es un tópico muy presente en el cine, ¿se busca hablar de ciencia por la llegada al público o simplemente porque es parte de nuestra vida ?

Con estas premisas, dialogaremos con el guionista de la película, Fernando Castets, y con el periodista especializado y productor Axel Kutchevasky, sobre el intenso diálogo que existe entre la ciencia y el cine, con particular interés en las neurociencias contadas desde la pantalla grande de manera masiva.

Aprovechamos la oportunidad para invitarlos a ver y volver a ver la película, que está libre y disponible en la plataforma cine.ar : https://play.cine.ar/INCAA/produccion/585

Spoiler Alert ! Durante el evento se mostrarán algunas escenas de la película

E-POSTERS

CELLULAR AND MOLECULAR NEUROBIOLOGY

Reduced GluN2A expression induces increased seizure susceptibility in vivo and augmented glutamate sensibility in vitro

Maria Florencia Acutain[1], Diana Jerusalinsky[2], Lucas de Oliveira Alvares[3], Maria Veronica Baez[1]

1. Laboratorio de Sinapsis y Neurobiologia Celular, Instituto de Biología Celular y Neurociencia (IBCN, UBA-CONICET), 2. Laboratorio de Neuroplasticidad y Neurotoxinas, Instituto de Biología Celular y Neurociencia (IBCN, UBA-CONICET), 3. Laboratório de Neurobiologia da Memória, Instituto de Biociências, Universidade Federal do Rio Grande do Sul (UFRGS)

Presenting Author:
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Synaptic plasticity involves changes in cytoskeleton proteins and postsynaptic receptors including NMDA receptors (NMDAR). These receptors are heterotetramers composed by two obligatory (GluN1) and two regulatory subunits, being GluN2A and GluN2B the most expressed in cognitive related brain structures. In the last years, grin2A mutations were associated with complex phenotypes that led to neurodevelopmental disorders which include the occurrence of seizures and in some cases, decreased GluN2A levels. In order to better understand the role of GluN2A reduced expression in synaptic plasticity and behavior, we induced a GluN2A knock-down (GluN2A-KD) in two models: primary mature hippocampal neuronal cultures and in the CA1 hippocampal region of young adult Wistar rats. In vivo, the GluN2A KD animals showed increased seizure susceptibility, induced after PTZ injection. Furthermore, in vitro, the GluN2A-KD neurons showed higher glutamate sensibility than control ones in calcium imaging assays, as well as, changes in dendritic branching and synapse number which were observed by immunofluorescence. Altogether, these results suggest that GluN2A down regulation, alter glutamate responsiveness and would facilitate seizure outcome that is a hallmark in patients carrying grin2A mutations.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Development of perisomatic inhibition in adult-born granule cells of the dentate gyrus: role of neuroligin-2

Andrea Aguilar-Arredondo[1], Ayelen I. Groisman[1], Alejandro F. Schinder[1], Damiana P. Giacomini[1]

1. Laboratorio de Plasticidad Neuronal, Fundación Instituto Leloir, Buenos Aires

Presenting Author:
***Andrea Aguilar**, aaguilar@leloir.org.ar*

Adult neurogenesis occurs throughout life in the mammalian hippocampus, and GABAergic signaling is necessary for the development and maturation of new granule cells (GCs) of the dentate gyrus (DG). We have recently shown that perisomatic inhibition by parvalbumin interneurons (PV-INs) becomes functionally mature in GCs aging >6 weeks. However, the molecular mechanisms that rule the establishment of this synapse remain unknown. We have investigated whether neuroligin-2 (NL2), a molecule involved in the development of inhibitory contacts, is involved in this process. First, we used confocal microscopy to characterize the development of synapses formed by PV-INs expressing tdTomato onto GCs expressing GFP. We quantified the area of perisomatic contacts at different time points and observed a substantial increase between 2 and 4 weeks, with no further changes at later time points. Next, we delivered a retrovirus to express a shRNA against NL2 and monitored the consequences of NL2 knockdown on the development and function of the PV-IN to GC synapse. We found no changes in the area of perisomatic inhibition in confocal images. However, electrophysiological recordings revealed immature features (slow kinetics) in both spontaneous and evoked postsynaptic currents in 6-week-old GCs with reduced NL2 levels. Our results reveal NL2 as a critical player for the functional maturation of perisomatic inhibition in developing GCs of the adult brain.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Aβ induces amyloidogenesis in human neurons through Gβγ subunit signaling

Magdalena Antonino[1], Paula Marmo[1], Alfredo Lorenzo[1], Alfredo Lorenzo[2], Anahí Bignante[1]

1. Laboratorio de Neuropatología Experimental. INIMEC – CONICET – UNC, 2. Departamento de Farmacología- FCQ- UNC

Presenting Author:
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Aggregation and progressive deposition of amyloid beta (Aβ) is a fundamental event in the pathogenesis of Alzheimer's disease (AD). The cleavage of the amyloid precursor protein (APP) by BACE1 is the most critical event in amyloidogenesis, although the mechanism and the intracellular compartment where this event occurs are still discussed. It has been reported that Aβ is capable of inducing its own production, but the mechanism is yet unclear. We hypothesized that the interaction of Aβ aggregates with APP, acting as its receptor, activates a signaling pathway mediated by Go/βγ that enhance the intracellular convergence of APP and BACE1 in amyloidogenic compartments, favoring Aβ production. Overexpressing a system of bimolecular fluorescence complementation (BiFC: APP-Vn and BACE1-Vc) in human neurons, we found that treatment with Aβ oligomeric (o-Aβ) increased BiFC intensity, effect that was abrogated by gallein, a pharmacological inhibitor of βγ signaling. Moreover, o-Aβ enhanced the BiFC intensity in Rab11-positive RE, effect that was avoided by gallein. Also, we found that Aβ treatments augmented amount of β-CTF and intracellular Aβ, and gallein abolished this increment. In conclusion, pathological aggregates of Aβ triggers an increase in the interaction of APP and BACE1 in RE and the production of β-CTF and Aβ intracellular in neurons, effect that is dependent of Gβγ signaling.

CELLULAR AND MOLECULAR NEUROBIOLOGY

The role of tau in the structure and function of the axon initial segment

Cayetana Arnaiz[1], Iván Fernández-Bessone[1], Trinidad Sáez[1], Mariana Holubiec[1], Sol Sargiotto[1], Elena Avale[2], Tomás Falzone[1]

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The axon initial segment (AIS) integrates synaptic signals, initiates action potentials, and acts as a selective barrier for axonal cargo. This region presents specific structural features, such as microtubule (MT) fascicles, Ankyrin-G (AnkG) and Spectrin linkers, and enrichment of ion channels. Tau, a MT-associated protein highly expressed in neurons, functions as a MT stabilizer and an axonal transport regulator. Recently, tau mutations and changes in expression levels have been associated with AIS defects. However, the molecular mechanisms by which tau modulates the AIS remain unknown. My work focuses on elucidating how tau regulates AIS structure and function. We used human neurons derived from iPSCs to perform tau conditional knockdowns (KD) and determined neuronal maturation by Sholl analysis and immunofluorescence. Interestingly, tau KD did not affect the dendritic arborization of human neurons, however AnkG revealed a distal shortening of AIS positioning. In addition, the effect of tau KD on the transport of the amyloid-precursor protein within the AIS was evaluated by live-imaging. Our preliminary results show that the techniques developed are suitable for our model and that we can quantify dynamic parameters as a readout of proper AIS function and structure. This work will provide knowledge on how tau modulates the AIS, which is essential for understanding the pathological tau effects associated with tauopathies.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Stress-induced vulnerability to develop cocaine addiction depends on cofilin modulation

María Julieta Boezio[1], Daiana Rigoni[1], María Paula Avalos[1], Andrea Guzmán[1], Mariano Bisbal[2], Liliana Cancela[1], Flavia Bollati[1]

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Actin dynamics in dendritic spines can be associated with the neurobiological mechanisms supporting the comorbidity between stress exposure and cocaine increase rewards. The actin cytoskeleton remodeling in the nucleus accumbens (NA) has been implicated in the expression of stress-induced cross-sensitization with cocaine. The main of the present study is evaluate the involvement of cofilin, a direct regulator of actin dynamics, in the impact of stress on vulnerability to cocaine addiction. Here, we show that the inhibition of cofilin expression in the NA core using viral short-hairpin RNA is sufficient to prevent the cocaine sensitization induced by chronic stress. Moreover, the reduced cofilin levels also impede a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor surface expression enhancement and promote the reduction of head diameter of spines in animals pre-exposed to stress after a cocaine challenge in the NA core. We report that cofilin downregulation prevents facilitation of the acquisition of cocaine self-administration (SA) in male rats pre-exposed to chronic stress. These findings highlight the role of cofilin in the neurobiological mechanisms supporting the comorbidity between stress exposure and addiction-related disorders.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Morphological alterations of a central auditory synapse in a mouse model with enhanced medial olivocochlear efferent activity

Daniela María Chequer Charan[1], Wenqing Huang[2], María Eugenia Gómez-Casati[3], Carolina Wedemeyer[1], Ana Belén Elgoyhen[1], Yunfeng Hua[2], Mariano Nicolas Di Guilmi[1]

1. Research Institute in Genetic Engineering and Molecular Biology (INGEBI), Laboratorio de Fisiología y Genética de la Audición, Buenos Aires, Argentina, 2. Shanghai Jiao Tong University School of Medicine, Ninth People's Hospital, Shanghai Institute of Precision Medicine, Shanghai, China, 3. Instituto de Farmacología, Facultad de Medicina. Universidad de Buenos Aires. Argentina

Presenting Author:
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The auditory system in many mammals is immature at birth but fine-tuned in adults. Spontaneous neural activity in the inner ear was proven to play a critical role in guiding this process. This is shaped by an efferent pathway that descends from the brainstem (the medial olivocochlear system, MOC) which transiently contacts the inner hair cells. In the knock-in mouse model with enhanced MOC activity (L9'T), altered functionality of auditory brainstem responses (Boero et al., 2019) and synaptic dysfunction of calyx of Held (CH) in the medial nucleus of the trapezoid body (MNTB) (Di Guilmi et al., 2019) have been observed at different developmental stages. Furthermore, our unpublished results of intracellular dye injection experiment revealed a delayed innervation refinement in L9'T MNTB principal cells during development. In this work, we set out a comprehensive structural investigation of the CH-type synapses from different tonotopic regions at P22-25 by means of large-scale 3D electron microscopy. We observed the presence of MNTB cells co-innervated by multiple CHs in both WT and L9'T mice with a slightly higher percentage of this phenotype in the L9'T (5/19 cells, 26%) than in the WT (4/22 cells, 18%). This was found mainly in the lateral MNTB region in the L9'T mice (Lat: 30%, 6/20 cells vs. Med: 26%, 5/19 cells). These results suggest a long-lasting impact of enhanced MOC innervation on the structural refinement of central auditory synapses persisting beyond hearing onset.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Changes in gene expression on the ventral hippocampus in a mice model of perinatal protein malnutrition and rescue by enriched environment: Relation with epigenetic mark 5-hydroxymethylcytosine

Carolina D Alberca[1], Ligia Papale[3], Andy Madrid[3,4], Reid Alisch[3], Eduardo T Cánepa[1,2], Mariela Chertoff[1,2]

1. Universidad de Buenos Aires. Facultad de Ciencias Exactas y Naturales. Departamento de Química Biológica, Laboratorio de Neuroepigenética y adversidades tempranas. Buenos Aires, Argentina, 2. CONICET- Universidad de Buenos Aires. Instituto de Química Biológica de la Facultad de Ciencias Exactas y Naturales. (IQUIBICEN). Buenos Aires, Argentina, 3. Department of Neurological Surgery, University of Wisconsin, Madison, WI, USA, 4. Neuroscience Training Program, University of Wisconsin, Madison, WI, USA,

Presenting Author:
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Perinatal protein malnutrition increases the risk to develop anxiety and depression. Studies in mice have shown that these altered behaviors can be rescued by and enriched environment (EE). The epigenetic mark 5-hydroxymethylcytosine (5hmC) is an environmentally sensitive DNA modification that is highly enriched in the brain and its association with gene expression is understudied. We previously analyzed the distribution of 5hmC on the ventral hippocampus in a mouse model of perinatal protein malnutrition (40% of the required amount of protein) and subsequent exposition to an EE after weaning. We observed that malnutrition is associated with low levels of this epigenetic mark 5hmC in genes related to the development of the CNS. Moreover, the exposure to an EE under the perinatal malnutrition model increases the level of this mark in genes related to those terms. In this work, we analyzed the genome-wide expression profile by RNAseq. A significant number of genes affected by malnutrition reverted their expression levels due to the EE. The changes in gene expression are observed mainly on neurons and astrocytes. Although the 5hmC mark does not appear to be associated with the transcription process under the malnutrition model, it may be regulating the transcriptional levels of genes affected by the EE. 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

Accelerated epigenetic aging in adults with Down Syndrome in the Argentine population

Giulia Solange Clas[1], Elmer A. Fernández [2], Juan Carlos Vázquez [2], Lucía Pertierra[1], Nahuel Magrath Guimet[1], Fernanda Tapajóz[1], Belén Helou[1], Tatiana Itzcovich[1], Micaela Barbieri[1], Horacio Martinetto[1], Gustavo Sevlever[1], Ricardo Allegri[1], Ezequiel Ignacio Surace[1]

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, 2. CIDIE - CONICET*

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***Giulia Solange Clas** , clas.giulia.s@gmail.com*

Life expectancy of individuals with Down Syndrome (DS) is currently 60 years. From age 40 they have an increased risk of dementia and almost all of them have histopathological features of Alzheimer's desease (AD) in their brains. Also, it is known that the ε4 allele of the APOE gene and the R47H variant of TREM2 increase the risk of AD. DS is also associated with a group of clinical manifestations of accelerated aging. DNA methylation-based biomarkers of ageing (epigenetic clocks) can be assessed by different models. It is known that DNA methylation age (DNAm) has a positive correlation with chronological age in disomic individuals while DS subjects exhibit an age acceleration effect in blood and brain. Here, we analyzed the acceleration in DNAm age in adults with DS using the Horvath's model and its correlation with cognitive impairment.
We determined the DNAm age of 7 participants with DS in peripheral blood leukocytes. Median age was 47 years. Variants in APOE and TREM2 were analyzed by RFLP-PCR.

Five participants exhibited the 3/3 genotype in APOE and two of them the 3/4. The R47H variant in TREM2 was not observed. Five participants showed a significant biological age acceleration and one participant's DNAm age was similar to his chronological age. Of note, one participant showed a deceleration in the DNAm age. We did not find a trend towards a greater presence of the risk allele ε4 or cognitive impairment in participants with a significant DNAm age acceleration.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Nrf2 signaling and cytoskeleton as targets of α-synuclein overexpression: new insights into pesticide-induced neurotoxicity.

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Overexpression of α-synuclein (α-syn) and pesticide exposure are considered triggering factors of Parkinson's disease. Previously we demonstrated that α-syn overexpression downregulates neurofilament light chain expression and alters actin organization in neuroblastoma cells. In this work, we studied the effect of α-syn overexpression in neuronal cytoskeleton organization and how this could affect the antioxidant response during pesticide-induced neurotoxicity. For this purpose, neurons stably expressing wild type α-syn gene (WT α-syn) were exposed to the pesticide Maneb (Mb). Overexpression of α-syn triggered actin polymerization and Tau phosphorylation. Cytoskeleton changes were associated with differential activation and subcellular localization of focal adhesion (FA) and LIM kinases, respectively. FAK and Tau phosphorylation and the expression of Nrf2-dependent antioxidant enzymes were increased by Mb exposure in WT α-syn cells. The upregulation of antioxidant defenses was associated with a neuroprotective effect against pesticide neurotoxicity. However, Nrf2 nuclear localization induced by Mb exposure was not altered by α-syn overexpression. Our results demonstrate that Nrf2 trafficking seems to be affected by cytoskeleton disturbances induced by WT α-syn overexpression. Further studies are necessary to decipher the crosstalk between cytoskeleton reorganization induced by α-syn overexpression and Nrf2-dependent signaling during Mb neurotoxicity.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Dissecting the putative differential roles of ghrelin-evoked versus constitutive growth hormone secretagogue receptor (GHSR) activity in mouse models

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The growth hormone secretagogue receptor (GHSR) is a G-protein coupled receptor highly expressed in the brain that mediates the action of the stomach-derived hormone ghrelin. In addition, in vitro studies have shown that GHSR displays a very high constitutive activity, whose physiological function remains uncertain. Here, we studied mice with genetic or pharmacological manipulations of GHSR in order to clarify the putative role of GHSR constitutive activity in vivo. First, we investigated mice harboring a mutant version of GHSR that lacks constitutive activity (GHSR-mut mice). We found that GHSR-mut mice show daily food intake and body weight similar to wild-type (WT) mice but did not increase food intake nor the expression of the marker of neuronal activation c-Fos in the hypothalamus in response to ghrelin. Also, GHSR-mut mice show high fat diet (HFD) intake in a binge eating protocol similar to WT mice, in contrast to GHSR-deficient mice which display reduced intake of HFD. Additionally, we assessed the effects of the selective GHSR inverse agonist PF-5190457 in mice. We found that PF-5190457 reduces the effects of ghrelin treatment on both food intake and c-Fos expression in the hypothalamus. Also, PF-5190457 reduced HFD intake in WT mice exposed to the binge eating protocol, while it was ineffective in GHSR-deficient mice. Thus, current results indicate that unmasking differential roles of ghrelin-evoked vs. constitutive GHSR activity in vivo is extremely challenging.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Glyphosate exposure impairs motor behavior and b-catenin expression in juvenile rats.

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Glyphosate is the active ingredient in the most widely used broad spectrum herbicides in the world. Even though numerous studies demonstrate the effects of Glyphosate based herbicides on developing mammals, the use of these formulations keeps expanding. The nervous system is highly affected by exposure to this compound. On this account, we study the effects of glyphosate exposure on brain developement and maturation in rats by in vivo and in vitro assays.

We used the rotarod test to evaluate motor coordination and balance in juvenile rats. Our results indicate that Glyphosate treatment caused a deficiency in these motor skills when compared to control groups. Considering previous studies, we then analyzed [?]-catenin expression in different brain regions such as frontal cortex, dorsal striatum and cerebellum by Western Blot. B-catenin is a crucial component of the canonical Wnt signaling pathway, which plays a major role in the central nervous system developement and functioning. Our results show that Glyphosate exposure leads to changes in the b-catenin expression pattern in developing rats. In addition, studies in mature cultured neurons also show alterations in the regulation of B-catenin expression when treated with glyphosate during a critical period of synpatogenisis.

Taken together, these findings suggest exposure to glyphosate during development induces motor dysfunctions, likely accompanied by a downregulation of the Wnt-B-catenin pathway.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Analysis of the potentiation mechanism of the α9α10 cholinergic nicotinic receptor by extracellular calcium.

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The α9α10 nicotinic cholinergic receptor (nAChR) is a pentameric cation-permeable ion channel that mediates the inhibitory synapse between efferent fibers and outer hair cells of the cochlea. Each nAChR subunit comprises a large extracellular amino-terminal domain, four transmembrane domains (TM1-TM4) and a long cytoplasmic loop between TM3 and TM4. 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 α9α10 nAChRs are potentiated by Ca2+ in the micromolar range and blocked at millimolar concentrations. In order to identify the structural determinants responsible for Ca2+ potentiation, 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 Ca2+. Moreover, we identified α10 E45 and E175 as key residues involved in this potentiation. These studies are being complemented with molecular dynamics simulations of the interaction of Ca2+ with different nAChRs models to help in the structural interpretation of the results.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Tetraspanins as key regulators of the hippocampal dendrite development

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The formation of synaptic connections during nervous system development requires the precise control of dendrite growth and synapse formation. Tetraspanins (Tspans), also called transmembrane 4 superfamily (TM4SF), represent a large family of proteins that participate in neuronal development. Several Tspans have been reported to regulate synapse formation, function and plasticity. Despite the progress obtained in recent years, little is known about the role of Tspans in the control of neuronal morphology and connectivity. Taking advantage of the postnatal expression of some Tspans by hippocampal developing neurons, we used gain and loss of function assays to examine how altered Tspan expression impacts dendrite morphology, filopodial and spine formation and maturation of primary hippocampal neurons. Here, we show that some under characterized Tspans could also regulate both dendrite complexity and dendritic spine density of hippocampal neurons. In the near future, it would be interesting to explore with more detail the role of these specific Tspans in hippocampal synapse formation and plasticity.

CELLULAR AND MOLECULAR NEUROBIOLOGY

CHARACTERIZING THE NANOSCALE ORGANIZATION OF THE ACTIN/ SPECTRIN MEMBRANE-ASSOCIATED PERIODIC SKELETON IN RODENT NERVES USING 3D-STORM MICROSCOPY

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It has been recently discovered that axons and dendrites possess a particular arrangement of their cortical skeleton, referred to as the Membrane-associated actin/spectrin Periodic Skeleton (MPS). The MPS is a periodic protein structure consisting of actin "rings" located transversely to the axon and separated every 190 nm by α/β-spectrin tetramers "spacers". The MPS can only be described using super-resolution (SR) microscopy approaches, since its spatial features lay below the diffraction limit of light. Most of published studies describe the MPS in vitro (in cultured neurons) and the precise organization of the spectrin “spacers” within each period is poorly resolved. We have thus begun a project to shed light into this in rodent nerve sections, that is, in situ, using 3D-STORM SR microscopy. We have first established a protocol for the examination of mouse optic and sciatic nerves preparations suitable for them by 3D-STORM. We have preliminary evidence for a model in which spectrin tetramers are arranged in each period at regular and fixed distances irrespective of axonal identity and that scales with axon diameter. We have also evidenced that the localization of a spectrin tetramer in one period is correlated with the position of tetramers in neighboring periods, suggesting a structural constrain for their interaction with actin rings. We believe that describing the MPS at the nanometer scale in situ will provide meaningful insights into its possible functions.

CELLULAR AND MOLECULAR NEUROBIOLOGY

The ketone body β-hydroxybutyrate (βHB) rescues behavioral defects in DAF-18/PTEN mutants of C. elegans

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Mutations in the phosphatase and tensin homolog (PTEN) gene, a negative regulator of the Akt/PKB pathway, are associated with neurodevelopmental disorders (NDDs). In recent years, ketogenic diets (KGDs) have been shown to have beneficial behavioral effects in animal models of NDDs. Ketogenic diets trigger a metabolic shift by forcing the production of ketone bodies (KBs) to generate ATP. The mechanisms underlying the beneficial effects of KGDs on NDDs are unknown. Here we used daf-18/PTEN mutants of C. elegans to gain molecular and cellular insights into the effects of KGDs on neurodevelopment. We find that these mutants are defective in exerting a complex behavior such as the escape response. These behavioral defects improve in animals cultured in the presence of KB β-hydroxybutyrate (βHB). Surprisingly, exposure to βHB at early stages is sufficient to achieve this improvement throughout adulthood, suggesting that βHB is necessary at a critical stage of development. We have also found that the effect of βHB is abolished in daf-16/FOXO mutants, revealing a key role for this transcription factor. Finally, we observed morphological defects in GABAergic motor neurons in daf-18 mutants. We are exploring whether exposure to βHB can amend these abnormalities. Given the high level of conservation of the pathways involved (PTEN/AKT/FOXO) across the animal kingdom, this work could contribute to better understand NDDs and establishing potential therapeutic options in mammals.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Gamma entrainment promotes adult neurogenesis in the aging hippocampus

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Non-invasive gamma entrainment using light stimulation at 40 Hz can reduce levels of amyloid beta peptide and improve memory performance in several mouse models of Alzheimer's disease. While light flickering was shown to increase the gamma frequency component of hippocampal oscillations, the mechanisms that transduce visual stimulation into cellular and circuit changes remain elusive. Because neurogenesis in the aging hippocampus is particularly sensitive to electrical activity, the effects of gamma entrainment might be revealed by analyzing its impact on developing new neurons. Using light flickering, we studied the impact of 40 Hz stimulation on the development of neurons born in the dentate gyrus of 8-month-old mice. Gamma entrainment boosted adult neurogenesis, as shown by a significant increase in doublecortin labeling, a marker for immature neurons. We also found that dendrites grow faster in developing granule cells from entrained mice, suggesting enhanced levels of connectivity. These preliminary results reveal that light flickering at 40 Hz awakes mechanisms that promote neuronal plasticity not only under pathological conditions, but also in the healthy aging brain.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Oxidative distress and Grx2 deregulation in Alzheimer disease

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From the factors proposed to be involved in Alzheimer's disease (AD) initiation and progression(1,2), oxidative distress, caused by an increase in reactive species produced particularly in the mitochondria, has been highlighted as a highly relevant process that mediates significant protein changes affecting neuronal function(3).
Glutaredoxins (Grx) are of utmost importance for the maintenance of the reduced state of proteins involved in relevant cellular processes; being key factors in redox regulation(4,5,6). Changes in redoxins levels have been associated with oxidative distress in AD(6). To test the association of increased oxidation and intracellular dynamic defects in the progression of AD we developed human brain organoids from iPSC control and APP Swedish mutation (APPSwe)(7,8). Our characterization of AD pathology showed, in APPSwe organoids, an increase in Aβ reactive area, as well as an increase in p-Tau levels using western blot (WB) and immunostaining techniques. WB analysis of TRXs levels showed a significant decrease of Grx2 expression in APPswe organoids. This result comes hand in hand with an increase in superoxide anion levels observed in live organoids with the APPswe mutation.
Our results highlight the relevance of modeling neurological diseases using complex tissue arrangements, and point to a deregulation in redox pathways in AD, which, if modulated, could be used as a therapeutic strategy for treatment of abnormal oxidation in this complex disease.

CELLULAR AND MOLECULAR NEUROBIOLOGY

nsSNPs within the extracellular loops of M6a impair its neuroplastic function

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The expression levels or polymorphisms within the GPM6A gene are associated with neuropsychiatric disorders such as schizophrenia, depression and claustrophobia. GPM6A encodes the neuronal membrane glycoprotein M6a, which promotes filopodia/spine and synapse formation in vitro. Even though strong evidence suggests that the extracellular loops of M6a (ECs) command its function, the molecular mechanisms linking M6a to the onset of such diseases remain unknown. To gain knowledge on this mechanisms, we aim to characterize new non-synonymous polymorphisms (nsSNPs) in the coding region of ECs of GPM6A. Preliminary results suggest that the mutants expression, subcellular localization and folding are not affected by the presence of nsSNPs. However, we identified nsSNPs that impaired M6a-induced plasticity in neuronal cultures and now we are focusing on the mechanisms by which the protein's function fails. In this sense, previous reports showed that M6a dimerization is necessary to induce filopodia and synapse formation. M6a´s ECs are involved in homo- and heterotypic protein-protein interactions and might lead to the formation of M6a oligomers at the plasma membrane. Thus, we are currently evaluating whether the nsSNPs might disturb the protein's oligomerization through number and brightness analysis (N&B), which allows us to monitor RFP-tagged M6a oligomer distribution in live cells.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Decoding the regulation of activity-dependent gene expression programs in neurons

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Activity-driven gene expression is necessary to implement synaptic plasticity mechanisms required to encode, store and retrieve long-lasting information. How neurons integrate and process neuronal activity patterns and translate them into specific activity-driven gene transcription programs is still not clear.
To address this question, we employed different neuronal activation protocols available in the literature that are known to elicit different specific patterns of neuronal responses: KCl depolarization, Bicuculline and Tetrodotoxin withdrawal. Taking advantage of the neuronal activity patterns generated by these mechanisms, we performed cortical neuronal primary cultures and stimulated neurons. Upon these protocols we extracted RNA and protein samples at different time points and performed RNA libraries and sequencing and western blot analysis.
Genome-wide analysis reveals distinct gene expression profiles and dynamics induced upon each neuronal activity pattern and phosphorylation dynamics of Ca2+ dependent proteins as ERK and p38 may explain part of these differences. Additionally, comparing 7DIV vs 21DIV cultures we found that neuronal maturational stage strongly influences the transcriptional response elicited by neuronal activation. We conclude that a neuron can differentially translate its activity into specific cellular programs that involve distinct gene expression and protein phosphorylation programs.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Development of a high throughput fluorometric assay with small-scale neurosphere cultures for the identification of factors that promote oligodendrogenesis.

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In demyelinating diseases, like Multiple Sclerosis, myelin is progressively lost due to oligodendrocyte damage. Since the identification of undifferentiated neural stem cells (NSC) with the ability to regenerate neural lineages, new potential alternatives have emerged for these pathologies.
In this work, by using transgenic mouse strains expressing green fluorescent protein (GFP), we developed a small-scale, high-throughput cell culture fluorometric assay that allows the identification of factors that could enhance oligodendrogenesis from NSC.
Dissociated neurospheres from ACT::GFP mice were used to optimize fluorometric detection of DNA content by Höechst staining and quantification of viable cells by GFP expression, using a multiplate fluorometer reader. Dissociated neurospheres from CNP::GFP mice, expressing GFP under 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase) promoter, were used for the detection of oligodendroglial lineage by the same fluorometric method. We found a 45% increment in GFP fluorescence after treatment with pro-oligodendrogenic factor PDGF-BB respect to controls, indicating that this method effectively detects the activation of oligodendrogenesis from NSC.
This novel approach could be used for the screening of large numbers of factors or drugs at different doses for the identification of possible candidates that promote oligodendrogenesis from NSC that could be used for the development of new therapeutical approaches for demyelinating diseases.

CELLULAR AND MOLECULAR NEUROBIOLOGY

LEAP2 Impairs the Capability of the Growth Hormone Secretagogue Receptor to Regulate the Dopamine 2 Receptor Signaling

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The growth hormone secretagogue receptor (GHSR) signals in response to ghrelin, but also acts via ligand-independent mechanisms that include either constitutive activation or interaction with other G protein-coupled receptors, such as the dopamine 2 receptor (D2R). A key target of GHSR in neurons is voltage-gated calcium channels type 2.2 (CaV2.2). Recently, the liver-expressed antimicrobial peptide 2 (LEAP2) was recognized as a novel GHSR ligand, but the mechanism of action of LEAP2 on GHSR is not well understood. Here, we investigated the role of LEAP2 on the canonical and non-canonical
modes of action of GHSR on CaV2.2 function. Using a heterologous expression system and patch-clamp recordings, we found that LEAP2 impairs the reduction of CaV2.2 currents induced by ghrelin-evoked and constitutive GHSR activities, acting as a GHSR antagonist and inverse agonist, respectively. We also found that LEAP2 prevents GHSR from modulating the effects of D2R signaling on CaV2.2 currents, and that the GHSR-binding N-terminal region LEAP2 underlies these effects. Using purified labeled receptors assembled into lipid nanodiscs and Forster Resonance Energy Transfer (FRET) assessments, we found that the N-terminal region of LEAP2 stabilizes an inactive conformation of GHSR that is dissociated from Gq protein and, consequently, reverses the effect of GHSR on D2R-dependent Gi activation. Our results provide critical molecular insights into the mechanism mediating LEAP2 modulation of GHSR

CELLULAR AND MOLECULAR NEUROBIOLOGY

Wnt7b stimulates axonal differentiation and development.

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In the nervous system, the establishment and maintenance of neuronal polarization is crucial for correct development and function. This asymmetry is generated in response to intrinsic and extrinsic signaling molecules. Wnts proteins are known regulators of cell polarity and has also been shown to be a symmetry-breaking factor in proliferating cells. In this study, we set out to investigate the role of Wnt7b signaling in the polarization of hippocampal neurons. We previously showed that Wnt7b affects the establishment of neuronal polarity and axonal outgrowth since Wnt7b stimulated neurons evidenced an increase in axonal length. We then focused our attention on short time Wnt7b treatment analyzing tau-1 immunoreactivity after 6 h in vitro. Surprisingly, we found that neurons exposed to Wnt7b showed higher tau-1 reactivity, a typical feature of axons, compared to controls. After that, we observed that Wnt7b stimulated neurons developed longer and more complex axon at 20 HIV. To go further, we examined the intracellular signaling pathway triggered by Wnt7b. Thus, Wnt proteins may signal through canonical or non-canonical pathway to modulate neuronal development and maturation. Pharmacological inhibition of JNK mediated non-canonical pathway abolished Wnt7b axonal effects. Consistently, we then observed that Wnt7b treatment increases the JNK activity at the axonal growth cone. Later studies evidenced that Wnt7b also increases microtubule stability around 30% compared to controls.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Differential effects of alpha synuclein on intracellular trafficking

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Alpha synuclein (AS) is a highly studied protein that is related to many neurodegenerative diseases such as Parkinson's disease and a group of pathologies known as synucleinopathies. AS normal function is debated but it is known that (1) participates in the regulation of the presynaptic vesicle reserve, (2) it could have a chaperone activity and plays a role in the assembly of the SNARE complex, (3) it can interact with Rab GTPases and (4) is involved in vesicle recycling. Despite being a focus of study, the mechanism by which AS generates pathogenic effects is unclear. One of the most interesting hypothesis is the one that postulates that AS could be affecting intracellular trafficking (Lindquist Lab 2006; experiments in yeast). This trafficking defects can result in decreased synaptic and surface protein exposure, lower trophic factor support, and less membrane trafficking. Altogether, these consequences could result in neurodegeneration. In our work we focus on the study of intracellular trafficking under the effects of AS in primary neuronal cultures. For this study we use a state-of-the-art system to synchronize the intracellular trafficking to analyze ER-Golgi-dendrites vesicle dynamics. Surprisingly, we found that AS induces a delay in the intracellular trafficking of a mainly axonal protein (p75NTR), while a dendritic protein (transferrin receptor) was not affected. These results sheds light on the mechanism by which AS may be acting in neurodegenerative diseases.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Increased anxiety-related behavior and neuronal spine density in a loss-of-function model of circular RNA

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Within the large family of non-coding RNAs there is a newly characterized class called circular RNAs (circRNAs). These transcripts mostly derive from exonic sequences and are the products of an alternative mechanism of splicing known as backsplicing. These products are single-stranded RNA molecules with covalently joined ends. Due to the high expression of numerous circular transcripts in nerve tissue samples, we have selected a circRNA derived from the Tulp4 gene to perform a functional characterization. To do so, we have generated a transgenic knock-out mouse line to model circTulp4 loss-of-function in vivo. CircTulp4-KO mice are viable and fertile but have alterations in excitatory neurotransmission.
More recently, we performed a neuronal morphological characterization through a microscopic quantitative analysis of brain sections from a Thy1-eGFP mouse line, where a sparse population of neurons express EGFP. We observed that circTulp4-KO mice do not differ in the complexity and total length of the dendritic arbor. However, we observed that KO mice have a higher dendritic spine density and a marginal increase in spine volume.
Furthermore, we made an extensive behavioral characterization of this mouse line. We found that circTulp4 loss-of-function led to hyperlocomotion under illuminated (stressful) conditions, increased startle response and an altered stress-responsivity. Together, these results suggest that circTulp-KO mice display an increased anxiety-related behavior.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Effects of a social and material deprivation murine model on gene expression in medial prefrontal cortex

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Embryonic development and early childhood are particularly vulnerable stages for neurodevelopment. Often, people who are disadvantaged during these stages live in contexts with many of the needs unsatisfied instead of facing an isolated type of difficulty. This is why we developed a murine model of social and material deprivation (SMD) that intends to reflect the complexity of people's different realities.
During the face validation of the model we found that the male pups of the SMD group were more dominant and more aggressive than their control counterparts.
The aim of this work was to analyze the consequences of the model on gene expression in the brain. We carry out this analysis in the medial prefrontal cortex (mPFC) due to its role in social behaviors. Since the excitatory/inhibitory (E/I) balance is important for this type of behavior, we began the exploration for genes related to the GABA- and glutamatergic pathways. In addition to that, given its role in neural plasticity, we also evaluated the expression of Immediate Early Genes (IEGs).
We found an increased expression in NMDA glutamate receptors in SMD mice and an increase in the expression of a serotonergic receptor in males .We did not find changes in IEGs nor GABA-related genes or AMPA glutamate receptors.
These results suggest that the treatment has effects on the E/I balance in the mPFC, which could explain the behavioural changes mentioned above. They also prompt further study of other areas of the brain.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Angiotensin II receptor´s immunolocalization in a model of Parkinson's disease

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Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by the selective death of dopaminergic neurons of Substantia nigra (SN). The presence of the Angiotensin II (Ang II) receptors has been described in SN. Overstimulation of AT1 receptors could produce oxidative stress, which affect the sensitive area of the SN. We utilized a rat rotenone model, which it was assayed previously by our group, to evaluate changes in the Ang II receptor´s localization in SN. Microparticles with the neurotoxin rotenone were administered by subcutaneous injection (dose of 50 mg/kg). Both Ang II receptors were detected with anti- AT1 and anti AT2 antibodies in brain cryostat sections. Immunohistochemical evaluation of tyrosine hydroxylase indicated that treatment with rotenone microparticles did have effect on dopaminergic neurons (a reduction about 33%). The density of AT1 positive cells was significantly lower in treated rats than in control animals ($p < 0.05$). AT1 receptors were localized mainly in a perinuclear region. While the density of AT2 positive cells showed no significant difference between treated and control animals. AT2 receptors predominantly exhibited cytoplasmatic and perinuclear localization. In coincidence with our previous results, we confirm the presence of both Ang II receptors in SN of rotenone model of PD. These findings are important to provide information about the potential role of brain renin angiotensin system in neurodegenerative processes

CELLULAR AND MOLECULAR NEUROBIOLOGY

Generation of a Drosophila melanogaster line for studying of the structural dynamics of the actin/ spectrin membrane-associated periodic skeleton in situ

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It has been recently discovered that axons and dendrites possess a particular arrangement of their cortical skeleton, referred to as the membrane-associated actin/spectrin periodic skeleton or MPS. The MPS is a periodic protein structure consisting of actin "rings" located transversely to the axon and separated every 190 nm by α/β-spectrin tetramers "spacers". It is speculated that a better understanding of the MPS organization, distribution and dynamics could shed light into understanding the biology of axons and dendrites. The MPS can only be described using super-resolution (SR) microscopy approaches, since its special features lies below the diffraction limit of light. All published approaches describe static pictures of the MPS in cultured neurons. On the contrary, we anticipate that studying MPS dynamics in tissue (in situ) will provide more relevant evidence on its possible functions. In order to do this, we present a plan for producing a Drosophila melanogaster line in which the endogenous single beta-spectrin gene will incorporate successive peptide tags in the C-terminus, in a cell- and time-specific manner. This animal model will allow us to study the dynamics of beta-spectrin within the MPS in situ. To do this, we will perform CRISP/Cas9-mediated gene editing of the beta-spectrin gene, so that it incorporates different terminal codons after recombination by Flippase and Cre, which can be controlled in time and space by existing fly lines.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Multiple states of neuronal development in the adult hippocampus revealed by single-nuclei RNA-seq

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Adult hippocampal neurogenesis plays a critical role in spatial memory formation and retrieval, context discrimination, and clearance of memory traces. In the mouse dentate gyrus, the maturation of adult-born granule cells (GCs) lasts several weeks and can be divided in 4 phases based on electrophysiological and morphological features. However, the molecular mechanisms that control the progression through those discrete phases are still unknown. We have proposed that such progression is driven by sequential changes in the program of gene expression, and should be revealed by transcriptome analysis. We thus set up an approach for high-throughput single-nuclei RNA sequencing applying Chromium 10X Genomics technology to interrogate the transcriptomic composition of new GCs at 1, 2, 4 and 8 weeks of age. We used double transgenic mice, Ascl1CreERT2;CAGfloxStopSun1sfGFP to allow conditional expression of Sun-1/sfGFP in the nuclear membrane of GCs at identified ages. Fluorescent nuclei were purified using FACS. We have obtained a dataset containing 18,000 distinct transcripts in 16,000 nuclei. Preliminary bioinformatic analysis resulted in multiple clusters corresponding to different stages of neuronal differentiation. Interestingly, radial glial cells move along a pathway of >12 transitions to reach a mature neuronal phenotype. We are currently identifying specific markers to discriminate possible functional differences among those clusters.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Role of the neuronal glycoprotein Gpm6a in differentiation of medial ganglionic eminence progenitors from human pluripotent stem cells

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The neuronal membrane glycoprotein M6a (Gpm6a) functions in the processes of neuronal differentiation and development and its function in the differentiation of neurons derived from mouse and human embryonic stem cells has been shown recently. Diverse neuropsychiatric diseases such as depression, schizophrenia, claustrophobia, Alzheimer's disease, and learning disability have been linked to the alteration in GPM6A expression levels or sequence.
In the present project we propose to employ technology human induced pluripotent stem cells (iPSCs) as an alternative approach to study the role of Gpm6a in neuropsychiatric disease in the human context. The central hypothesis to be tested is that the Gpm6a functions in differentiation of medial ganglionic eminence (MGE) progenitors and neurons derived from human iPSCs. MGE progenitors serve as precursors to GABA interneurons and basal forebrain cholinergic neurons (BFCNs), two cell types that are relevant in numerous neuropsychiatric diseases such as schizophrenia, autism, intellectual disabilities, and Alzheimer's disease, among others.
Our aim is to use iPSCs differentiated into MGE progenitors to study functional consequences of the presence or absence of Gpm6a in the development of human brain tissues. Here iPSC lines will be generated and differentiated toward MGE progenitors and endogenous Gpm6a expression will be evaluated by qPCR and immunocytochemistry throughout the course of neural differentiation of iPSCs.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Pharmacological GluN2A antagonism blocked CAMKII activation thought not GluN1 increased levels after chemical LTP induction

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Synaptic plasticity (SP) involves changes in dendritic spine cytoskeleton, volume, and postsynaptic molecular composition. One of the most studied forms of SP is Long Term potentiation (LTP) that induces dendritic spine maturation and change in NMDA Receptor (NMDAR) composition. It was described that GluN1, and GluN2A NMDAR subunits increase 70 minutes after LTP induction or memory acquisition. GluN2A is considered a marker of mature synapses, however, little is known about its role in LTP induction in part because GluN2A antagonists, as NVP 0077, are recently developed. In our laboratory, we induced chemical LTP in hippocampal cultured neurons and then blocked the GluN2A subunit by NVP-0077. Later, we analyzed molecular dendritic composition by immunofluorescence assays. Preliminary, we found that NVP-0077 blockade inhibits GluN2A but not GluN1 increased dendritic levels 70 minutes after LTP induction. Also, at this time point we observed that CAMKII is not activated, and NF-kB levels are similar to basal levels. Further investigation is needed to establish that GLuN2A increased levels post LTP induction would be a marker for this process.

CELLULAR AND MOLECULAR NEUROBIOLOGY

SPONTANEOUS ELECTRICAL ACTIVITY REGULATES AXONAL ARBOR MATURATION, GROWTH AND TERRITORY IN DEVELOPING ZEBRAFISH LATERAL LINE AFFERENT NEURONS

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Proper assembly and function of developing sensory circuits requires the combination of genetic programs and spontaneous electrical activity (SEA). In order to decipher the mechanisms by which SEA regulates the establishment 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 neuromasts, which contains 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 (AN) exhibit SEA between 5- and 7-days post-fertilization (dpf), however is unknown if it plays any role in the assembly of the LL system. We silenced SEA in single LL AN by stochastic over-expression of inward rectifier K+ channels and analyzed the phenotype and the dynamics of axonal arbor growth. Suppression of SEA in single LL AN led to a decrease in axonal arbor complexity and innervation area in the hindbrain. Moreover, silenced neurites display higher motility as well as higher formation and elimination rates than WT ones, which are features of immature neurons. Our results provide an in vivo demonstration that SEA regulates axonal arbor maturation, growth and territory in the hindbrain, in developing LL AN.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Different modes of ASIC1a activation and downstream signaling

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Acid-sensing ion channels (ASICs) regulate synaptic activities and play important roles in neurodegenerative diseases as well as pain conditions.
Classically, ASICs are described as transiently activated by a reduced pH, followed by desensitization; the activation allows sodium influx, and in the case of ASIC1a-composed channels, also calcium to some degree.
The channel has been recently shown to be activated through a molecule present in the Texas coral snake venom. The finding was associated with the activation of the channel at neutral pH via the toxin and causing intense and unremitting pain.
By using different pharmacological tools, we analyzed the downstream signaling pathway triggered either by the proton and non- proton activation of ASIC1a-composed channels in in vitro models.
We show that the non-protonic mode of activation determines the activation of the ERK signaling cascade at a higher level and duration compared to the proton mode.
This study adds to the growing evidence of the important role ASIC1a channels play in different physiological and pathological conditions and also hints at a possible pathological mechanism for a sustained effect.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Enriched environment reduces food intake and body weight modulating the hypothalamic NPY/GHSR system.

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The enriched environment (EE) is a model of inanimate and social stimulation that reduces adiposity and improves glucose tolerance and eating behavior. Our objective was to study the effects of EE on the brain homeostatic system that regulates food intake. For this, male Wistar rats were exposed on postnatal day 21 (PND) to EE (collective cage of 14 rats with different toys, n=14) or standard environment (SE, cage of 4 rats without toys, n=14). Body weight and food intake were monitored weekly until sacrifice at PND90, when the weight of epididymal adipose tissue (EAT) and brain were obtained. The arcuate nucleus (ARC) of hypothalamus was isolated using the Palkovits micro-punch technique. The gene expression of orexigenic neuropeptides [Agouti related protein (AgRP) and neuropeptide Y (NPY)], anorexigenic neuropeptides [amphetamine and cocaine regulated transcription (CART) and proopiomelanocortin (POMC)] and leptin (Ob-Rb) and ghrelin (GHSR) receptors were measured by RT-PCR. The results showed that the EE group presented a reduction in food intake after the first week and a lower body weight from the second week of the experiment. At PND90, the EE group had 7% less body weight (p=0.0004) with no differences in the EAT. In ARC, the EE group presented lower levels of expression of NPY (p=0.034) and GHSR (p=0.019). In conclusion, EE disrupts the NPY/GHSR system and alters the homeostatic regulation of food intake, leading to a decrease in food intake and body weight.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Studies about the cooperative signaling between p75NTR and Trk receptors in the modulation of choroidal angiogenesis

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The p75 neurotrophin receptor (p75NTR) is a transmembrane protein that mediates neuronal growth, survival and death. p75NTR can couple to different co-receptors to transduce intracellular signals. New evidences point p75NTR as a key player in the development of vasculopathies. Our results show that p75NTR increases 7 days post laser in retinal glia and RPE (retinal pigment epithelium)-choroid infiltrate (f4/80+) of mice with choroidal neovascularization (CNV). The deletion of the receptor reduced CNV and prevented photoreceptor dysfunction. It has been reported that p75NTR can potentiate Trk signalling in some scenarios. Thus, we aim to determine if p75NTR modulates Trk activation to modify neovessel formation in a mouse model of laser-induced CNV. In order to estimate Trk activation, we performed western blot assays to detect the activation of one of its downstream pathways: MAPK/ERK. We detected decreased expression of phosphor-ERK in CNV mice respect to control, both in retina and in RPE-choroid 7 days post laser. Immunostaining did not show localization of pan-Trk nor p-ERK in retinal glia identified by GS and GFAP respectively. Similarly, no overlapping was observed between pan-Trk and RPE-Choroid infiltrate. Surprisingly, p75NTRKO mice showed increased expression of p-ERK 7 days after laser in retina and RPE-Choroid. In sum, our results suggest that the formation of vascular tufts in CNV is not mediated by the cooperative signalling between p75NTR and Trk receptors.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Protective Effect of Nitro-Oleic Acids in Oxygen-Induced Retinopathy

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Inflammation and oxidative stress are involved in neovascular retinopathies (NR). 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) modulates the antioxidant response and has a cytoprotective effect in NR. An Oxygen-Induced Retinopathy (OIR) mouse model was used. OIR mice were intraocular (i.o.) injected at P12 with 5 µM of NO2-OA or vehicle and intraperitoneal (i.p). at P14, P17, P20, P23 with 15 mg/Kg of NO2-OA or vehicle. At P17 or P26 mice were sacrificed. Some eyes were fixed to obtain whole mount for microscopy and other retinas were used for Western blot or RT-PCR assays. The electrical activity of the retina in response to a light stimulus was measured by scotopic electroretinography (ERG). Amplitudes and latencies of a- and b-waves from scotopic ERG were recorded at P17 y P26. Whole mounts showed that NO2-OA induced the vascular regrowth and decrease the pathological neovascularization at P17. In addition, Western blot of neural retinas showed significant changes in proteins involved in neurotoxicity and stress glial (GS and GFAP) at P17 in OIR mice treated with NO2-OA respect to vehicle. At P26 NO2-OA prevented the decrease in b-wave amplitude as well as the diminished expression of total Caspase-3 protein in P26 OIR. These findings suggest that NO2-OA could be beneficial or cytoprotective for retinal cells in NR.

CELLULAR AND MOLECULAR NEUROBIOLOGY

GABAergic Signaling in the Aging Cerebellum and the Influence of Membrane Cholesterol Dynamics

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Membrane lipids undergo changes that directly impact lipid raft dynamics, which in turn affect downstream receptor-mediated signaling. Some of these oscillations occur during brain aging and are associated with the onset and progression of neurological disorders. Here, we analyzed the levels of major neuronal lipid classes, protein expression, and their interactions at the cell surface in young and aged rat cerebella. We focused on members of the GABAergic system: the heterodimeric GABAB receptor and KCC2, the transporter responsible for modulating the strength of ionotropic GABAAR-mediated currents. GABABR subunits and KCC2 are present in multiple isoforms in the old cerebellum, as our UHPLC-MS/MS analysis has confirmed. By applying WB and IHC, we observed that GABAB2 subunit levels decrease with aging. We further explored and compared membrane lipid profiles using TLC, and we discovered that cholesterol content increases significantly with age. By performing Co-IP, we observed that GABABR and KCC2 partially cluster within the same macromolecular protein complex in both groups, but the magnitude of the interaction fluctuates according to age. Then, we investigated how the GABABR-transporter complex responded to changes in the ratio of cholesterol to phospholipids by simulating their molecular dynamics using a neuronal membrane model. Our results suggest that cholesterol levels impact protein-protein interactions of the GABAergic system, as present in the cerebellum.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Effects of phenylalanine incorporation into the C-terminus of alpha-tubulin on axonal transport

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Phenylketonuria (PKU) is a metabolic disorder caused by a deficiency in the phenylalanine hydroxylase enzyme, resulting in the accumulation of phenylalanine (Phe). Elevated plasma levels of Phe cause microcephaly, epilepsy, permanent intellectual disability, delayed development, and motor disorders. These symptoms appear to be a consequence of neuronal cell loss, dendritic simplification and synaptic density reduction.
Tubulin, the protein constituent of microtubules, is subjected to removal and re-addition of the tyrosine (Tyr) residue encoded at the C-terminus of its α-chain, and there is increasing evidence of the role of this post-translational modification in various specialized microtubule functions. We have previously demonstrated both, in vitro and in vivo, that Phe can be cyclically incorporated and released from α-tubulin, with kinetics similar to those of Tyr . Now, we examined the effects of Phe treatment on different cellular parameters. We observed alterations in mitochondrial transport along the axon of hippocampal neurons and changes in the distribution of these organelles. In addition, we found abnormal interactions between Phe-enriched microtubules and molecular motors that participate in organelles transport. Our findings could be relevant for the brain dysfunctions observed in PKU patients since the proper intracellular distribution of mitochondria is crucial for neuronal development, synaptic transmission and plasticity.

CELLULAR AND MOLECULAR NEUROBIOLOGY

Copper increases oxidative stress and Cholesterol synthesis in astrocytes

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It was described that high cholesterol (Cho) levels in membranes favor theamyloidogenic processing of the amyloid precursor protein (APP)in patients with Alzheimer's disease (AD). Also, Cu may raise the levels of reactive oxygen species (ROS)leading to the production of pro-inflammatory cytokines and the nuclear translocation of SREBP-2. This transcription factor enhances the transcription of genes such as 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and the LDL receptor (LDLR) and thus increases Cho levels.
Astrocytes provide Cho to neurons and become reactive in conditions of neuroinflammation such as in AD, overexpressing glial fibrillary acidic protein (GFAP).
We study the effects of sub-lethal concentrations of Cu exposure on Cho synthesis and the redox status in astrocytes primary cultures of male rats.
We evaluate: Cu concentration; Cho de novo synthesis and total Cho; LDLR and GFAP protein levels; HMGCR,TNFα and SREBP2 mRNA levels, and the redox status by the analysis of TBARS, NOx, protein carbonyls (PCs), and SOD activity.
Data show an increase in HMGCR, SREBP-2 and LDLR, and higher levels of Choafter Cu treatment. Treatment also riseTNFα and GFAP levels. Finally, astrocytes expose to Cu show higher levels of TBARS, NOX, and PCs than control cells. In addition, SOD activity enhancesafter treatment. Our data suggest that Cu addition favor Cho synthesis and uptake in astrocytes in vivo, as well as promote their reactivity.

CHRONOBIOLOGY

Motivation for food reward is involved in food anticipatory activity in mice under restricted feeding conditions

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In mammals, the circadian system modulates several behavioral and physiological processes, including the response to natural rewards such as food. On the other hand, when food is temporally restricted, animals display an anticipatory food activity (FAA) that is controlled by a food-entrainable oscillator (FEO).
We have previously shown that mice under a 12:12 light/dark (LD) cycle exhibited a diurnal rhythm in motivation for food reward, becoming more motivated during the night (active phase). This rhythm was also evident under constant dark (DD) conditions, indicating the endogenous nature of this modulation.
In this work, we present evidence that motivation for food reward is involved in FAA regardless of mice being food restricted during the day or night phases of the LD cycle. Mice in a restricted feeding (RF) protocol under a 12:12 LD cycle were allowed to consume food only 3 hours during daytime or nighttime. Then, motivation behavior was assayed - through the progressive ratio (PR) schedule - in two different time points: during FAA (i.e, two hours before food availability) and in the opposite phase to wich the RF was carried out. Our results show that mice are highly motivated to work for food reward when FAA is present regardless of the time of day. These results suggest that, during FAA, components related to reward pathways might be activated and consecuently generate an increase in motivation bypassing circadian time cues.

CHRONOBIOLOGY

Circadian disruption induced by tumor development in a murine model of melanoma

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Dysfunctions in clock-controlled body functions, such as sleep disorders, as well as deregulation of clock gene expression or glucocorticoid levels has been observed in cancer patients. Moreover, these disorders have been associated with a poor prognosis. This work explored the circadian rhythms at behavioral and molecular levels in a murine melanoma model induced by subcutaneous inoculation of B16 tumoral cells. We observed that the presence of the tumors induced a decrease in the sturdiness of the locomotor activity rhythms and in the amount of night time activity together with a delay in the acrophase and in the activity onset. Moreover, these differences were more marked when the tumor size was larger than in the initial stages of the tumorigenesis protocol. In addition, serum glucocorticoids, which have strong clock-controlled rhythms, lost their circadian patterns. Similarly, the rhythmic expression of the clock genes Bmal1 and Cry1 in the hypothalamic Suprachiasmatic Nuclei (SCN, the central clock) were also abolished in mice carrying tumors. Altogether, these results suggest that tumor-secreted molecules (tumor macroenvironment) could modulate the function of the central circadian pacemaker (SCN). This could account for the worsening of the peripheral biological rhythms such as the locomotor activity or the serum glucocorticoids. The knowledge of the circadian rhythms in cancer patients could be useful to improve their quality of life. Moreover, since the deregulation

CHRONOBIOLOGY

EFFECTS OF PIOGLITAZONE-RETINOIC ACID ON DAILY RHYTHMS OF RC3 AND GAP43 IN THE HIPPOCAMPUS OF Aβ-INJECTED RAT

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Alzheimer's disease (AD) is the most frequent form of dementia in older people. Elevated levels of beta-amyloid(Aβ) peptide causes oxidative stress which lead to a gradual impairment of memory. Neurogranin(RC3) and neuromodulin (GAP43) play an important role in the learning and memory. Pioglitazone(Pio) and retinoic acid (RA) have antioxidant properties. In addition, pioglitazone improved cognitive performance in Alzheimer's patients. Previously, we have demonstrated that an icv injection of Aβ(1-42) modified the daily rhythms of oxidative stress parameters and cognition-related factors in the hippocampus of rat. Continuing with that study, the objective of this work was to evaluate the effect of Pio/RA on RC3 and GAP43 expression as well as on Aβ protein levels, lipid peroxidation and protein carbonyls throughout a 24 h period, in the hippocampus Aβ-injected rat. Four-month-old male Holtzman rats divided into the groups control, Aβ-injected and Aβ-injected treated with Pio/RA were maintained under 12h-light12h-dark conditions. RC3 and GAP-43 mRNA levels were determined by RT-PCR. Lipid peroxidation and protein carbonyls levels were determined by colorimetric assays. Aβ protein levels were analyzed by immunoblotting. We found that Pio/RA reestablished rhythmicity of those temporal patterns. These findings might constitute, at least in part, molecular and biochemical basis of restoration of circadian rhythmicity by the administration of Pio/RA in neurodegenerative disorders.

CHRONOBIOLOGY

OUR CLOCKS IN PANDEMIC: A STUDY ON THE DISRUPTION OF CIRCADIAN RHYTHMS AND ITS RELATIONSHIP TO SUNLIGHT EXPOSURE AND DIGITAL DEVICE USE DURING THE COVID-19 PANDEMIC.

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Our biological rhythms are of great importance and their dysfunction can cause disruptive effects on sleep, affecting our performance in various activities and human health. The quarantines adopted due to the COVID-19 pandemic produced several changes in our daily lives, reducing exposure to sunlight and altering the schedules of our social activities. For this reason, and because these are the main factors affecting our biological rhythms, the present study is based on the idea that the quarantine carried out in Argentina affected our circadian rhythms. Additionally, it was thought that the use of digital devices has increased and exposure to sunlight has been reduced, which are other important factors that may alter the biological clock. In the present study, we propose to take a new look at our biological clocks in the pandemic, emphasizing the importance of their optimal functioning and their link to human health.

CHRONOBIOLOGY

Aging modifies the circadian rhythms of Sirt1 and DNA repair enzymes expression in the rat cerebellum. Effect of caloric restriction.

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Caloric restriction (CR) attenuates the aging process. The circadian molecular machinery and metabolism communicate through Sirtuins. SIRT1 plays a vital role in maintaining genomic integrity, through regulation of the BER repair pathway. We investigated whether in the Sirt1, Ogg1 and Ape1 expression have a temporal pattern in the rat cerebellum, the consequences of aging and the effect of a calorie restricted diet. Male Holtzman: young (3-mo-old), old (22-mo-old) rats fed ad-libitum; and old-CR (22-mo-old rats fed at 40% calorie restricted diet for the last three months) were used. Sirt1 expression showed a circadian oscillation, peaking at night in the cerebellum of the young, aging phase advanced the rhythm of Sirt1 (CT16:07±00:37 vs CT01:31±00:07, p<0.01), while in the old-CR, rhythm's acrophase came near to control values (CT20:07±00:06, p<0.01). No circadian variation was found in the Ogg1 and Ape1 mRNA levels in the young, however, we observed maximal levels at CT4 and CT20, respectively (p<0.05). Ogg1 and Ape1 expression showed a circadian rhythm in the old, with the acrophase occurring at the beginning of the subjective day (CT01:57±00:11 and CT01:09±00:10, respectively). CR phases delayed Ogg1 and Ape1 rhythms in the old-CR (CT13:17±00:03 and CT07:41±00:35, respectively). Our conclusion is that there is a temporal variation in the expression of Sirt1, Ogg1 and Ape1 in the young rat cerebellum, which is altered by aging, and differentially modified by CR.

CHRONOBIOLOGY

EFFECTS OF PIOGLITAZONE-VALPROIC ACID ON DAILY RHYTHMS OF LIPID PEROXIDATION AND ANTIOXIDANT ENZYMES IN AN AB(1-42) INDUCED RAT MODEL OF ALZHEIMER DISEASE

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Alzheimer's disease (AD) is a primary cause of dementia in the elderly. It is determined by the deposits of Aβ which leads to memory impairment, oxidative stress associated to a deficient antioxidant defense system. AD patients also show alterations in their circadian rhythms. Numerous studies have shown that Pioglitazone (Pio) possess antioxidant properties and Valproic Acid (VA) improved cognitive deficits in an experimental model of AD. Taking into account these observations, the objective of this study was to evaluate the effect of Pio/VA, on the 24h rhythms of lipid peroxidation, as well as on catalase (CAT) and glutathione peroxidase (GPx) expression and activity and Bdnf/TrkB expression in the hippocampus of Aβ-injected rats. Four-month-old males Holtzman rats were divided into three groups defined as: 1) control 2) Aβ-injected 3) Aβ-injected treated with Pio-VA. Rats were maintained under 12h-Light:12h-Dark conditions. Lipid peroxidation levels were determined by colorimetric assays and CAT and GPx enzymatic activities by kinetic assays. CAT, GPx and Bdnf/TrkB transcript levels were determined by RT-PCR in hippocampus samples isolated every 6 h. We found that the treatment of Pio-VA reestablished rhythmicity of those temporal patterns. These findings might constitute, at least in part, molecular and biochemical basis of restoration of circadian rhythmicity by the administration of Pio-VA in neurodegenerative disorders.

CHRONOBIOLOGY

Studying the role of GABA in the regulation of sleep/arousal behavior

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It has been previously proposed that GABAergic inputs to the large lateral ventral neurons (lLNvs) of Drosophila may be responsible of informing those highly integrative arousal neurons about the sleep homeostat status. Meanwhile, the current paradigm proposes that the main circadian pacemaker of the Drosophila brain, the small lateral ventral neurons (sLNvs), have only minor influence in the control of sleep behavior.
Starting from this point, our aim is to describe the mechanisms of GABAergic inhibition in both sLNvs and lLNvs, their influence on sleep behavior and their role on the sleep homeostat. For this, we have performed specific genetic manipulations and quantified sleep behavior under basal and sleep deprivation conditions. Moreover, we have collected electrophysiological recordings to identify the extent of the role of the neurotransmitter GABA in the neuronal circuit studied, given that our final goal is to describe this network in detail.
Our findings confirm that the lLNvs receive information about the sleep homeostat status via the GABAA receptor Rdl through a complex neuronal circuit. They also suggest that the sLNvs are involved not only in the control of the circadian sleep timing but also, through GABAergic inputs, can regulate the quantity and quality of sleep.

CHRONOBIOLOGY

Microglia changes in the aging pineal gland: a view from the endolysosomal system

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Microglia are multifunctional immune cells within the brain. In the circadian pineal gland (PG), these phagocytes interact with other cell populations and constituent elements to finely modulate their development and function. As long-lived cells, microglia participate in changes that occur during normal aging, such as alterations in the architecture and functionality of subcellular organelles. Herein, we studied the expression pattern of the lysosomal and associated compartments marker ED1/CD68 in the PG from old male Wistar rats by using multiple immunofluorescence staining followed by quantitative confocal microscopy. Our results showed that the pineal Iba1+ cell population is composed of different subtypes according to the arrangement and cytoplasmic distribution of ED1, in both 3- and 18-month-old samples. However, our quantitative analysis revealed significant changes in the relative density of each phenotype with respect to age. To evaluate the functionality of the different ED1+ structures, we studied the expression of the lysosomal protease cathepsin D. Immunoreactivity for this enzyme in the aged PG suggests that microglia with ED1+ bodies might retain certain proteolytic capacity. Our results indicate that the pineal microglia themselves undergo many changes across their lifespan, including their phagocytic capacity. Microglia, as a plastic and resilient cell population, may continue to influence PG homeostasis and function even as the PG ages.

CHRONOBIOLOGY

Regulation of circadian clocks in C. elegans by clock gene homologs

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Circadian rhythms are endogenous oscillations adapted to environmental factors (Zeitgebers) which allow the biological clock to be adjusted to a 24-hour cycle. The circadian clock is based on clock genes that interact with each other to generate a transcription-translation feedback loop (TTFL). The output produced by the central clock is transmitted through neuronal/neuroendocrine signals throughout the body. Caenorhabditis elegans is a powerful model which offers an extensive set of molecular genetic tools to study the function and interaction of central clock proteins. In this work, we focused on the study of three proteins, LIN-42, KIN-20 and AHA-1, which are homologous to the mammalian and Drosophila clock genes PER, Casein Kinase 1δ/ε and BMAL-1, respectively. We studied how circadian rhythms are affected in strains carrying mutations in putative clock-related proteins, by means of a bioluminescent reporter system. Mutations in the three proteins induced a longer period compared to the wild type strain (close to 24 h): Lin-42 full deletion (26,41 ± 0,47 h, n=32), KIN-20 mutant (26,61 ± 0,69 h, n=39) and AHA-1 mutant (27,14 ± 0,61 h, n=36). In addition, the mutants exhibited a large phase change (> 3 h) when transferred from LD to DD cycle. In summary, our results allow us to obtain a better understanding of the proteins involved in the central clock of the adult nematode.

COGNITION

Behavioral analysis of a novel olfactory discrimination task in a visual context in head-fixed mice

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The ability to learn that a sensory stimulus signals a reward or punishment is one of the brain functions most critical for adaptation and survival. How animals integrate information about learnt sensory stimuli with spatial context and animal internal state is not completely understood. Here we developed a learning paradigm to evaluate the influence of spatial context on the association of an odor with a reward. Water-restricted mice were trained to perform an olfactory discrimination task under head-fixed conditions, whereby animals learn to drink water or not depending on the virtual visual context in which odor is presented. We show that animals reached to criterion within a few sessions. Learning was sequential, at first animals learn the position of the reward, then to discriminate between odors, and finally to discriminate between visual context, suggesting a difference in stimuli salience. We analyze three behavioral variables that change along learning: licking, sniffing and locomotion speed. Since an appropriate response to odor helps animals adapt to changing environments, we also studied how flexible is this behavior. We carried out a reversal learning protocol where the odor rewarded was changed, in the same context as before. Results showed that it took between 2-4 sessions to reverse the behavior. Therefore, we developed a behavioral paradigm suited to probing the neural basis of spatial context modulation of an olfactory-based behavior and its flexibility.

COGNITION

Neural modulation of feeding behaviors in C. elegans

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Feeding is a complex behavior controlled by environmental and internal physiological factors. The nervous system modulates motor activity depending on the availability of food and the nutritional state. When animals find food after a fasting period, they stay in a small area to exploit the new source of nutrients. Biogenic amines, serotonin (5-HT) and norepinephrine (NE) are involved in the modulation of food-related behaviors in mammals. However, the molecular mechanisms underlying this regulation are not entirely clear. Given its simplicity and highly conserved neurological pathways, C. elegans is a powerful organism that can be used to provide insights into the neural circuits modulating feeding behaviors.
When starved worms find food, 5-HT is released to decrease locomotion and promote food intake. We found that mutants lacking tyramine (TA), NE analog in invertebrates, are hypersensitive to the slowing-down response upon food encounter, resembling starved worms. This suggests that 5-HT and TA exert antagonistic effects. Moreover, the activity of tyraminergic neurons decreases in absence of food. In addition, serotonergic activity is enhanced in TA-deficient mutants. These results allow us to hypothesize that the inhibition of the tyraminergic activity during fasting favors the exacerbation of 5-HT-dependent effects on refeeding. Given the conservation in neuronal components, it is likely that our studies are significant to understand feeding behaviors in other animals.

COGNITION

THE IMPACT OF TIME, AGE AND FREQUENCY OF USE ON RECOGNIZING PERSONAL ITEMS OF OUR CLOSEST ONES: FORENSIC IMPLICATIONS. PRELIMINARY RESULTS

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Sometimes people have to recognize belongings of close ones that were found in places where, for example, genocides took place. This is done in order to pinpoint a missing person's last whereabouts and in some cases because the family asks to keep with their belongings. To do this, one part of the process is asking the relatives of the missing person to identify the items. However, in some cases (e.g. the missing people during the last Argentine military dictatorship) these procedures have been put in doubt by the legal system in order to prevent errors such as two or more families recognizing the same item as their own and thus to prevent nonsense re-exposure to traumatic memories. To the best of our knowledge, there is a lack of studies evaluating our performance on recognition of clothes from close ones. It is known that our capacity to correctly recognize items depends on various factors, such as age, time from acquisition, frequency of item exposure, level of stress, sleep, among others.
Here, we will discuss preliminary data of how different factors such as time, age and frequency of use modulate the capacity to correctly and falsely recognize personal items of close ones. These results can enlighten and help the everyday practice of organizations such as the “Argentine Team of Forensic Anthropology”(EAAF) to make decisions about the reliability of the clothing recognition by the victim’s relatives.

COGNITION

REGULAR PHYSICAL PRACTICE INFLUENCES THE EXECUTIVE FUNCTIONS AND EMOTIONAL MEMORY OF YOUNG ADULTS

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Exercise is a recurrent physical activity (PA) to obtain benefits at organic level. Nowadays, many investigations have found a relationship between PA and cognitive health. The aim of the current study was to evaluate if the amount of PA people does could affect their executive functions (EF) and emotional memory (EM). Fifty-four Young adults (18 to 60 years old) engage in two studies. Participants were divided regarding to their exercise compromise: low (LC), medium (MC) or high (HC). In the first study (n = 30; presential), EF were evaluated through Stroop test and Trail Making test. Regarding memory, participants observed pictures with emotional or neutral content; next immediate and deferred free recall and recognition were evaluated. In the second study (n = 24; virtual) the EF were evaluated with Hayling test; for memory task participants listened emotional and neutral words, after that free recall and recognition were evaluated (immediate and deferred). Results of study two didn't show significant differences. Nevertheless, in the study one, participants in MC and HC recalled more stimuli in the immediate memory task than participants in LC, besides MC had the best performance in the deferred evaluation. In addition, MC and HC groups showed better executive performance than LC. Many factors, such as the procedure used, can affect individuals' behavior and, therefore, explain the divergent result between studies. Future research could explore these effects deeply

COGNITION

Differential role of kinases in behavioral-tagging process of aversive memory formation after spaced learning

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Spaced trainings are more efficient than massed ones to induce long-term memories (LTM). Thus, even weak trainings can achieve LTM if proper spaced protocols are applied. Here we examined the temporal constraints and cellular processes underlying LTM formation by retraining using weak inhibitory-avoidance (wIA) task. A single wIA training is unable to form LTM assessed 24 h later, but two identical wIA sessions spaced by 15 min to 6 h inter-trial intervals, achieve LTM tested at 24 h. This promotion depends on hippocampal protein synthesis and the activity of ERKs, CaMKII and PKA kinases. We analyzed these results under the Behavioral Tagging (BT) hypothesis which postulates that trainings induce "learning tags" in activated neural sites, and there, new synthesized plasticity-related proteins (PRP) are used to form LTMs. We propose that spaced trainings stimulate the same neural populations allowing the additive effect of cellular mechanisms (e.g. ERKs activation) triggered by each session to reach the threshold required for PRP synthesis. Such addition would not occur if neural populations activated by each session differ. Then, combining wIA and spatial-object recognition (wSOR) sessions, did not result in LTM for either task. Our results suggest that LTM promotion via spaced wIA-trainings occurs by BT mechanisms, where ERKs are involved in PRP synthesis but not in tag setting, CaMKII is only involved in tag setting, while PKA is required for both processes to form LTMs.

COGNITION

EFFECT OF SHORT AND LONG-TERM ETHANOL INTAKE AND NOISE EXPOSURE IN ADOLESCENT MALE RATS: BEHAVIORAL DATA

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Adolescence, a period in which complex behavioral skills develop, can be influenced by environmental agents such as ethanol (EtOH) and noise. Therefore, the aim of this work was to evaluate possible EtOH and noise-induced alterations, using different schemes.
Adolescent male Wistar rats were subjected to voluntary consumption of EtOH during intermittent 24-hour periods for one or two weeks, using the two-bottle choice paradigm (5% EtOH/1% sucrose). A subgroup was exposed to noise (2h, 95-97 dB) after the first week. All animals were evaluated on different behavioral tasks and ETOH intake was measured.
Results showed that noise exposure was able to impair performance in associative memory (AM) and to increase anxiety-like behaviors (Anx) when evaluated at short-term. On the other hand, animals subjected to EtOH intake showed an increase in risk assessment behaviors (RABs) and exploratory behavior (EB). When EtOH was ingested before noise exposure, Anx decreased and RABs increased. In contrast, at long-term, animals exposed to either noise or EtOH showed a decrease in AM and an increase in Anx. In noise-exposed animals, including those also subjected to EtOH intake, an increase in EB was additionally observed. In conclusion, these results suggest that exposure to EtOH or noise might induce differential behavioral changes and that co-exposure can generate more behavioral changes in long when compared with short-term schemes, probably due to the greater amount of EtOH consumed

COGNITION

Effectiveness of computerized cognitive training in patients with diagnosis of mild cognitive impairment (MCI) using an argentinian videogaming platform: a double-blind randomized trial in Mar del Plata.

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Dementia is today one of the leading causes of disability. In Argentina, 23% of elderly people presented some cognitive impairment before the pandemic and it is estimated that prevalence increased with the lockdown. Mate Marote (MM) is an Argentine open source software specifically designed to train executive functions. It was tested in 5-8 year olds with excellent results. We have already evaluated the feasibility of the platform and made changes to improve its usability. Given the current needs, it is especially important to evaluate the efficacy of this tool en MCI. We are conducting a double-blind, randomized, controlled trial. A total of 60 patients >65 years with a diagnosis of MCI will be recruited and randomly assigned (1:1)to either the trained group or the control group. The trained group receives 60 individual sessions of ECC in 6 months. Assessments on cognitive abilities were conducted at baseline (T0) immediately after the intervention (T1) and six months after the intervention (T2) by an investigator who is blind to treatment assignment. The change in these assessments is the primary outcome measure but we evaluate different aspects of daily living as well. So far 35 patients have been recruited. The mean age is 76.9 (SD±5.6). 65% are women.The mean schooling is 11.17 years (SD±4.7). To date, only 6 patients have completed the comparative evaluation (T0 and T1), so the statistical calculations of the hypothesis test will not yet be performed.

COGNITION

Rebuilding the brain's dictionary: interaction between old and new meanings

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Word knowledge can be updated not only by the acquisition of novel words, but also by the learning of new meanings for words with established meanings. We are interested in determining the interaction between the original and the new meanings. Compared to learning novel word forms, it was previously proposed that memory for new meanings could be initially boosted during acquisition whereas an interference pattern between old and new meanings may appear later during consolidation (Fang et al., 2018). In the present study, native Spanish speakers (18-35 years old) learned novel meanings for 20 words of intermediate frequency (e.g., 'Scarf': A bird that doesn`t sing), and 48 hours later they performed a memory test. The study was performed online. Our results showed that while no advantage of familiarity was obtained regarding long-term memory retention of new meanings, a significant increase in learning efficiency was found compared to novel words. Thus, learning new meanings for old words takes significantly less time compared to learning novel words. Ongoing studies are analyzing the perturbation of the original meaning using a semantic decision task. The next step will analyze the role of a reactivation stage before the learning task. The central hypothesis is that the process of reactivating the memory of words would be a fundamental tool for updating definitions, allowing greater integration and less interference between the different meanings.

COGNITION

Dorsolateral Entorhinal Cortex in the destabilization/reconsolidation Process of Fear Memories

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The Dorsal Hippocampus (DH) and the basolateral complex of the Amygdala (BLA) are brain structures critically involved in the destabilization/reconsolidation process. Interestingly, BLA exerts a modulatory role over the structural plasticity of DH during said process. However, there is no direct connection between the two structures. The entorhinal cortex, particularly the dorsolateral region (dl-CEnt) is a parahippocampal structure regarded as the main input of the Hippocampus, and potentially an operational intermediate for the emotional information between both brain areas.
It the present work we explored the role of the dl-CEnt, trough pharmacological manipulation, in the destabilization/reconsolidation of fear memories as a step in outlining and further understanding the neural circuit between BLA and DH.

COGNITION

Retrieval as a key process to promote the persistence of spatial memory induced by spaced learning

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Here, we use the Spatial Object Recognition (SOR) task to study the mechanism underlying the persistence of long term memory (LTM) after spaced learning. A weak SOR (wSOR) training induced short but not LTM, whereas a strong SOR (sSOR) training formed a 1 but not 7 days LTM. Significantly, adding a wSOR-retraining session 1 day after sSOR training, promotes SOR-LTM persistence tested at the 7th day. We observed that the retraining session is only effective when the memory is liable to be expressed. Emetine, Rapamycin and the ERKs1/2 inhibitor U0126 blocked SOR-LTM expression administered before a test session, and these drugs infusion in the dorsal hippocampus before retraining impaired the LTM persistence. The amnesia induced by Eme and Rapa, but not by U0126, could be reverted by an open field (OF) exposure after retraining. We analyzed these results under the Behavioral Tagging hypothesis (BT) which postulates that the formation of lasting memories relies on the setting of a learning tag and the synthesis of plasticity-related proteins (PRPs). Thus, our results suggest that blocking ERKs activity at retraining impaired the tag setting, because PRPs provided by OF exposure did not rescue LTM. We postulate that retraining will mainly reactivate the sites labeled by the original learning, where the PRPs needed for memory expression and/or induced by retrieval, would be used to sustain the synaptic plasticity for establishing a persistent mnemonic trace.

COGNITION

ARE SHORT-TERM MEMORY GENES INVOLVED IN TIME ESTIMATION?

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The neurobiological basis of time estimation has not been clearly established yet. One hypothesis proposes that it encloses cognitive processes such as attention, learning, working memory, and decision-making. Considering that, time estimation could be a type of short-term memory in which the sole stimulus of time itself is enough to launch the behaviour. In an attempt to understand how the brain processes and utilizes temporal information in the second to minute range, we developed an interval timing experimental setup in Drosophila melanogaster. The core of our experiments is the motivation to drink a sucrose drop that is available for 10 seconds at a fixed interval of 60 seconds. We analyse the animal proboscis extension response (PER) over time. Results showed that training increases the time until PER, anticipating the occurrence of the drop. We operationally define time-referenced memory as a statistically significant increase in PER at the testing interval compared to PER average in the first three intervals. Here we investigate if genes already known to be involved in short-term memory mechanisms are also engaged in time estimation, beginning by sarah. Sarah is a serine/threonine phosphatase that regulates calcineurin activity. We will downregulate sarah both chronically and acutely over mushroom bodies by expressing its RNAi, to study learning and memory. If we confirm sarah's involvement in time-referenced memory we will continue with the calcineurin pathway.

COGNITION

Effect of early ethanol exposure during prenatal or neonatal period upon neonatal ultrasonic vocalizations and ethanol consumption

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Introduction. Gestational or neonatal ethanol exposure produce high affinity to ethanol's positive and anxiolytic effects promoting subsequent ethanol's consumption. Pup's ultrasonic vocalizations (USVs) -distress isolation calls- have been poorly studied in contrast to the well-defined USVs in adult rats. Moreover, when considering the anxiolytic effects of ethanol upon the emission of USVs, little attention has been paid to these effects on drug exposure during early life.

Aim. To analyze separation-induced distress vocalizations in neonate rats and their ethanol consumption as a function ethanol exposure during late gestation period or during the first week of postnatal life.

Methodology. During gestational days 17-20, dams received a subcutaneous injection of D-penicillamine (50 mg/kg) or saline (0.9% NaCl). Thirty minutes after, rats received an intragastric administration of ethanol (2.0 g/kg) or water. At postnatal days 4 and 6, pups received intraoral infusions of either milk or milk mixed with ethanol through an artificial lactation test. This test was followed by 5-min USVs recordings.

Results. At PD6 pups prenatally exposed to ethanol emitted more USVs during the last bin of evaluation compared with water group. In contrast, the postnatal experience with the drug during this day generating fewer USVs compared to groups that received milk. Ethanol consumption was increased in those pups prenatally exposed to the drug compared with water-exposed controls.

COGNITION

Molecular mechanisms involved in object recognition memory consolidation in the retrosplenial cortex

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We recently demonstrated that the retrosplenial cortex (RSC) is required for object recognition (OR) memory consolidation. Therefore, we decided to assess the molecular mechanisms involved in OR memory consolidation in this structure. We had previously observed an increase in c-Fos levels in the RSC 1 h after OR training (TR) session. Consistent with that, here we found that general protein synthesis is required for 24 h OR memory consolidation in the RSC. Furthermore, we infused c-Fos antisense (ASO) or missense (MSO) oligonucleotides into the RSC to study c-Fos requirement for memory consolidation. c-Fos ASO infusion had an amnesic effect at 24 h when infused 40 min, but not 4 h, before TR session. We then study the involvement of MMP-9, which is known to depend on AP-1 (conformed by c-Fos) transcriptional activity, this time we did not observe an effect in 24 h memory after MMP-9 ASO infusion 40 min before TR. Nevertheless, when re-tested the animals 7 d after TR we did observed remote memory amnesia in the ASO infused group. Our results show the requirement of c-Fos activity to trigger OR long-term memory consolidation and that MMP-9 is essential for OR remote memory.

COGNITION

Recurrent Ca2+ activity spatial configurations in a mushroom body-like structure of a crab during ongoing and elicited activity

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Insect mushroom bodies are well-known high-order associative centers. We have reported structural and physiological evidence to support the hypothesis that crustaceans possess structures equivalent to the mushroom bodies. The hemiellipsoid bodies of the crab Neohelice granulata exhibit many insect-like mushroom bodies traits, including neuroanatomical characteristics and plasticity that reflect the context dependent attribute of an associative memory. Previously, we have found overlapping but distinct spatial patterns elicited by visual or mechanical stimulation in the lobed region of the hemiellipsoid body (10.1002/cne.24960). Here, we used calcium imaging recordings to analyze the dynamic of the spatial configuration of the neural activity in the calyx-like (proposed input) region. Results showed, revealed by K-mean clustering of pictures representing the activity pattern for each calcium event during both ongoing and stimuli (visual and mechanical) elicited activity, several related recurrent spatial configurations of neuronal activity. According to crustacean's equivalent mushroom bodies calyces structure, the recurrence of these spatial configurations suggests different network elements (neuronal populations and/or neuronal processes) innervated by segregated multimodal inputs. These data further support the complexity of these structures, and suggest that stimuli elicited activity might rely on functional ensembles already operating in this center's ongoing activity.

COGNITION

Identification of brain structures involved in juvenile social play and affected by prenatal exposure to valproic acid

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social and communication deficits and repetitive patterns of behavior. We have previously found that male mice prenatally exposed to 600 mg/kg valproic acid (VPA) show reduced play solicitation at postnatal day 21. We hypothesized that these differences in behavior are
correlated with alterations in the activity and function of specific neuronal networks. Identification of such neurons may be relevant to our understanding of VPA effects on mouse behavior, and to ASD pathophysiology. To identify the brain structures involved in juvenile social play, we sacrificed VPA exposed and control animals 1.5h after a 30min session of play with a same-treatment, non littermate mouse. Animals were perfused with paraformaldehyde, and their brains processed for immunohistochemistry. We will analyze the expression of the early gene cFos in coronal sections throughout the brain. We will particularly focus on cFos expression in the prefrontal cortex (PFC) and the striatum, as previous reports have shown neuronal activation after social play in the anterior cingulate, prelimbic, infralimbic and orbitofrontal cortex, and in the dorsal striatum and nucleus accumbens. In addition, we will identify the type of neurons activated in each structure by co-immunofluorescence staining with the dopamine receptor 2 in the PFC and dopamine and cAMP-regulated phosphoprotein 32 (DARPP-32) in the striatum.

COGNITION

Facial recognition of emotions in refractory epilepsy of the temporal lobe, the role of the right angular gyrus (preliminary results).

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The facial recognition of emotions (FRE), ability to identify emotional states in others, is processed by temporo-fronto-occipital areas of the right hemisphere. In patients with drug resistant temporal lobe epilepsy (TLE) this function can be affected. This study seeks to assess whether TLE patients are impaired at FRE, and whether they perform the task recruiting alternative brain networks. Patients with right TLE (RTLE) (N=8), left (LTLE) (N=16), and controls (CTRL) (N=15) were evaluated by fMRI using stimuli with different facial expressions (joy, anger, fear, neutral, and baseline). At the behavioral level, there were significant differences in reaction time (RT) for joy stimuli between the groups: both TLE groups had longer RT compared to CTRL [F(2,40)=4.264,p=.021]. At the neural level, the contrast FRE of negative stimuli revealed that CTRL and LTLE activated similar areas in the calcarine gyrus, the lingual gyrus, and the cuneo, although the LTLE group had additional in frontal gyrus. The FRE of joy in CTRL, revealed frontal-parietal activations in the right angular gyrus that did not appear in RTLE. Preliminary results highlight the importance of the right angular gyrus in FRE for joy, possibly due to its involvement in the Theory of Mind (ToM) network, as ToM is needed to decode emotions. Also, FRE for joy is more complex to process than negative emotion, because it is link with empathy and ToM. We are currently increasing the sample size.

COGNITION

Is metacognition predicted by ASD traits in a neurotypical sample?

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by behavioral difficulties in social communication and social interaction, as well as restrictive or repetitive interests or behaviors. It is currently debated whether people with ASD have altered metacognition, defined as the ability to evaluate one's own cognitive processes in various domains. Currently, the results are mixed. While some studies suggest that metacognition is impaired in ASD, other studies have not observed differences compared to neurotypical participants. The main goal of this study was to contribute to this debate, through the study of metacognition in ASD traits in a sample of neurotypical individuals using an online experiment and a bias-free measure of metacognition. Preliminary results will be discussed.

COGNITION

Dream content during lucid dreams and out-of-body experiences, differences and similarities.

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During sleep, humans experience offline visual content that we call dreams, which are typically emotional and lack rational judgment about their strangeness. However, during lucid dreaming (LD), subjects know they are dreaming and can control the dream content. Another type of awere dream experience is the out-of-body experience (OBE) initiated from sleep paralysis. Although the differences between non-LD, LD and OBEs are evident, there is no record in the literature of such differences in dream content and some researchers describe OBEs as a type of LD. We conducted interviews with subjects who experienced LD and subjects who had OBEs frequently. A portion of them kept a dream journal for two months with precise instructions on how to write down their dreams. The collected dreams were analyzed by automatic methods of analysis of emotions such as EmoLex and Sentisense, also with classifiers such as Empath. The dream stories provided by the participants were scored with a series of ratings using a method based on Hall and Van de Castle's dream content scoring system upon which we developed variations and additional measures to adapt to the requirements of our task. The scoring was divided into sections, thought/emotion/action, presence of entities/characters and social interactions, sensory descriptions, spatial references, fantasy content, among others. Here we present the preliminary progress of this study of oneiric content.

COGNITION

Structural differences between non-lucid, lucid dreams and out-of-body experience reports assessed by graph analysis

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It has been recently found using graph theory that measures of network structure can predict ratings of dream complexity, where increases in connectedness and decreases in randomness are observed in relation to increasing dream report complexity. This approach proved to be useful to differentiate dream reports in the pathological population as well as NREM and REM dream reports but it has not yet been used to study the differences between different oneiric experiences. In this work we analyse dream reports that include non-lucid, lucid dreams and out-of-body experiences initiated from sleep paralysis. The reports are presented as directed graphs, where each different word plays the role of a node, and consecutive words are connected by a directed, unweighted edge. We analyse different network measures to compare the graphs. Preliminary results presented here suggest that both local measures, such as the degree of nodes, and global measures, such as clustering and the number of strongly connected components, allow for a categorization of different dream experiences.

COGNITION

EXPLORING THE RELATIONSHIP BETWEEN METACOGNITION AND DYSFUNCTIONAL PERSONALITY TRAITS

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Metacognition is defined as the capacity to evaluate one's own cognitive processes in various domains. Its relation with dysfunctional personality traits is still unknown, although it has been suggested that some personality disorders have difficulties knowing their own mental states. This relation has only been recently studied on an experimental level. Nevertheless, these studies have only used biased measures of metacognition. The present research aims at contributing to the study of the relationship between metacognition and dysfunctional personality traits. We ran an online perceptual decision making task with neurotypical adults along with the Personality Inventory for DSM-5 (PID-5). The preliminary results obtained are discussed, which will provide valuable information about the relationship between metacognition and dysfunctional personality traits.

COGNITION

A single dose of an antidepressant disrupts fear memory reconsolidation in mice

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Threatening experiences can lead to traumatic memories and cause post-traumatic stress disorder (PTSD). Under certain conditions, the retrieval of a stable consolidated memory destabilizes it triggering an active re-stabilization process called reconsolidation. During this unstable phase, memory can be vulnerable to interference by several pharmacological agents. In this work, we evaluate in mice whether a single dose of the antidepressant fluoxetine (Flx, 10 mg/kg i.p.) can disrupt contextual fear memory by blocking reconsolidation. First, we administered Flx after a brief exposure (3 min) to the training context (reactivation procedure) and measured freezing behavior when mice were re-exposed to the training environment one day later. Second, we investigated the effect of Flx administered 6 hours after reactivation or in its absence and found no effect on freezing behavior compared with vehicle injection. Flx-induced amnesia lasted for at least 3 weeks after training. We found no difference in the effect of Flx between male and female mice. Our findings indicate that a single systemic dose of Flx selectively disrupts the reconsolidation of a contextual fear memory. Given that current PTSD treatments involve long and emotionally exhausting procedures, blocking the reconsolidation of traumatic memories by a single dose of an antidepressant could be a starting point for developing a promising short and effective treatment for PTSD.

COGNITION

HOW THE PANDEMIC AND THE VIRTUALITY AFFECTED THE LEARNING PROCESS?

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Recent models have proposed a Bayesian approximation for understanding pedagogical situations (Shafto et al, 2008) in which a knowledgeable teacher chooses limited examples with the objective of having a learner infer a concept. How does prior information about the teacher's identity and his or her teaching strategies would affect learners' inferences of new concepts? Moreover, in the current context of remote education, are there any differences in this effect?
We present a new paradigm, based on the Rectangle Game in which a teacher helps a learner to find a secret box on the screen using a limited set of cues. Young adults were placed in the learners' role knowing (or not) that they were receiving cues generated by a teacher (2nd, 4th or 6th graders).
Our preliminary face-to-face interactions results indicate that (1) performance increases when playing consecutively with the same teacher and (2) knowing the teachers' age is significantly useful when there is no other information available, but it seems to be overshadowed by the knowledge acquired along the trials about the teachers' particular strategies. Our ongoing results suggest that knowing the teacher's age has a less significant value. Instead, subjects seem to rely exclusively in the quality of those strategies used by their teachers.
Our preliminary results strongly suggest that we do not learn in the same way in a remote education or a face-to-face context.

COGNITION

Effect of short term high-fat diet in contextual fear memory and structural plasticity. Possible modulation by alpha-melanocyte stimulating hormone (α-MSH).

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Cognitive deficit and neurodegenerative diseases are associated with age, however environmental factors such as chronic consumption of a high-fat diet (HFD) aggravate them in young and adults. The effects of HFD on the central nervous system (CNS) could be related to neuroinflammation, and even the consumption of HFD for a short period of time can exacerbate the inflammatory response to a mild immune challenge. Alpha-melanocyte stimulating hormone (α-MSH) mediates antiinflammatory and neuroprotective actions. We explored whether short-term (5 days) HFD consumption plus a mild immune challenge (LPS 10μg/Kg), potentiated the neuroinflammatory response in the hippocampus leading to cognitive deficits and possible changes in hippocampal structural plasticity. Our results show that short-term HFD does not affect body weight, however, produces changes in total cholesterol. HFD impaired contextual fear (hippocampal dependent) memory in rats that received LPS. This effect was associated with a decrease in spine density in the dorsal hippocampus (DH). The treatment with α-MSH (0.1μg/0.25μl) in the DH reversed the effect of short-term HFD in both contextual fear memory and in spine density.
Our present results indicate that HFD consumption for a short period sensitizes CNS to a subsequent immune challenge and produces impairment in the contextual fear memory that could be related to changes in hippocampal structural plasticity. α-MSH could have a protective effect.

COGNITION

IGF-1 GENE THERAPY ON DOPAMINERGIC NEURONS AND GLIAL CELLS INTERACTION IN EARLY COGNITIVE DEFICITS IN RAT PARKINSONISM MODEL

Macarena Lorena Herrera[1], Leandro Gabriel Champarini[1], Eugenia Falomir Lockhart[2], Franco Juan Cruz Dolcetti[2], Matías Jávega Cometto[3], Sofía Cervellini[2], María José Bellini[2], Claudia Beatriz Hereñu[1]

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Parkinson´s disease is a neurodegenerative disorder with a progressive dopaminergic (DA) neuronal loss and a variety of non-motor symptoms, such as cognitive dysfunctions. IGF-1 neuroprotective effects could be, in part, due to changes in the activity of neurons and glia. Aims: 1) to determine the early cognitive decline and the correlation of hippocampal changes in 6OHDA model, 2) to carry out therapeutic approaches with IGF-1 and 3) to analyze modifications on glial cells through different brain areas involved in the proposed circuit. Male Wistar rats were divided into 6 groups according to CPu bilaterally injection with 6OHDA or vehicle (SHAM) and the adenoviral therapy in hippocampus with RAd-DSRed or RAd-IGF1. At 3 weeks, rats were tested for behavioral tasks of cognitive performance and locomotor activity induced by amphetamine. Then rats were perfused, the brains fixed and IHC performed for TH and Iba-1 and GFAP for glial cells. Results: At 20 days post-lesion, memory deficits were observed in 6OHDA rats compared to SHAM rats. This cognitive decline was partially modified with IGF1 gene therapy. We observed changes in GFAP+ astrocytes in different dorsal hippocampus areas, mainly in the group with IGF-1 and changes of TH expression. IGF-1 gene therapy restored memory impairments and modified cellular activity. Knowledge of this potential therapeutic strategy with IGF-1 gene therapy motivates us to further studies under this experimental model

COGNITION

IGF-1 GENE THERAPY ON DOPAMINERGIC NEURONS AND GLIAL CELLS INTERACTION IN EARLY COGNITIVE DEFICITS IN RAT PARKINSONISM MODEL

Macarena Lorena Herrera[1], Leandro Gabriel Champarini[1], Eugenia Falomir Lockhart[2], Franco Juan Cruz Dolcetti[2], Matías Jávega Cometto[3], Sofía Cervellini[2], María José Bellini[2], Claudia Beatriz Hereñu[1]

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Parkinson´s disease is a neurodegenerative disorder with a progressive dopaminergic (DA) neuronal loss and a variety of non-motor symptoms, such as cognitive dysfunctions. IGF-1 neuroprotective effects could be, in part, due to changes in the activity of neurons and glia. Aims: 1) to determine the early cognitive decline and the correlation of hippocampal changes in 6OHDA model, 2) to carry out therapeutic approaches with IGF-1 and 3) to analyze modifications on glial cells through different brain areas involved in the proposed circuit. Male Wistar rats were divided into 6 groups according to CPu bilaterally injection with 6OHDA or vehicle (SHAM) and the adenoviral therapy in hippocampus with RAd-DSRed or RAd-IGF1. At 3 weeks, rats were tested for behavioral tasks of cognitive performance and locomotor activity induced by amphetamine. Then rats were perfused, the brains fixed and IHC performed for TH and Iba-1 and GFAP for glial cells. Results: At 20 days post-lesion, memory deficits were observed in 6OHDA rats compared to SHAM rats. This cognitive decline was partially modified with IGF1 gene therapy. We observed changes in GFAP+ astrocytes in different dorsal hippocampus areas, mainly in the group with IGF-1 and changes of TH expression. IGF-1 gene therapy restored memory impairments and modified cellular activity. Knowledge of this potential therapeutic strategy with IGF-1 gene therapy motivates us to further studies under this experimental model

COGNITION

Can we be “out” of our body? Characterization and clinical implications of out-of-body experiences during sleep paralysis: Preliminary results.

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Sleep paralysis is defined as a period of transitory immobility which occurs during sleep onset or offset. It is characterized by the inability to perform voluntary movements when the person feels awake and conscious about the environment. During an episode there may also be different types of hallucinations: The Intruder, characterized by the sense of an evil and threatening presence, and in some cases visual and tactile hallucinations. The Incubus, characterized by pressure on the chest and other body parts, breathing difficulties, feelings of suffocation, choking, pain and morbid thoughts of imminent death. Unusual body experiences which includes Illusory Movement Experiences (IMEs) and Out of Body Experiences (OBEs). IMEs are vestibular sensations such as the sensation of rolling or floating, and/or motor sensations of displacement without a visual component. The OBEs are an altered state of consciousness, defined as the experience in which an observer perceives the world from a point of view outside of their physical body. Unlike the other two components (incubus and intruder), during IMEs and OBEs the person may not feel body paralysis, and they are considered as "pleasant". OBEs during sleep paralysis can occur spontaneously, or they can be induced by training. Here, we will discuss preliminary results of an online survey with subjects who had unusual sleep experiences, such as OBEs and Sleep Paralysis and its clinical implications.

COGNITION

Semantic changes due to the COVID-19 pandemic from a large-scale word association study

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We investigate how the meaning for words changed as a function of the COVID-19 pandemic. Since the start of the pandemic, familiar words such as 'bubble' have acquired new senses (now used to refer to a group of people with whom one has frequent social contact). A widely used tool to study internal representations and processes involved in word meaning is the word association task, in which a word (i.e., the cue) is presented and the subject has to respond with the first word that comes to mind (i.e., the response). Here we report on a large-scale experiment of word associations that already had pre-pandemic data, Small World of Words, SWoW (De Deyne et al., 2019) and analyzed the modifications in the representations of 600 words. First, we determined the frequency and entropy for 'pandemic' words (words that incorporated new meanings or changed their frequency) and control words that were given as responses, at two different times: before pandemic (t0) and during pandemic (t1). Preliminary results show that pandemic words present greater differences in frequencies and entropy between t0 and t1 compared to control words, showing that the former are given as a response more often and to a more heterogeneous set of cues during the pandemic. In addition, we will measure semantic similarity within each word at the two time points and predict that pandemic words will present smaller similarities between t0 and t1, compared to control words.

COGNITION

Synaptic homeostasis and fake news

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The spread of "fake news" has become a major problem for societies around the world since the popularization of the internet and social media, which increased the ability to create and share information. Recent work showed that when people see invented news, can believe and even generate a memory of these false events, that is, fake news are capable of generating a false memory, and this occurs especially when the content of the fake material is consistent with ideology. On the other hand, it has been observed that there are individual factors such as analytical thinking ability, reasoning style or cognitive abilities that influence the generation of these false memories. Besides, a recent study found that decision-making is a result of the combination of the person's chronotype and the sleep pressure they have at the time of the evaluation. In this work we hypothesize that people's sleep pressure when observing fake news is a predictor of the ability to generate false memories about fake news. To study this, we developed a set of fake news that was presented mixed with real news. Our results indicate that people with higher sleep pressure tended to remember more fake news as they had really happened, than people with low pressure. We discuss these results in terms of the theory of synaptic homeostasis.

COGNITION

Differences in impulsivity among adolescent and adult rats in a self-paced rewarded task

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Adolescence is a gradual period of transition from childhood to adulthood. In this stage, subjects exhibit characteristic behaviors, such as increases in social interactions, novelty-seeking and risk-taking behaviors. In previous work of our lab, we found age-related differences in the performance of a self-paced rewarded task. Briefly, rats needed to withhold an action sequence for 2.5 s in order to obtain a reward. These experiments showed that adolescents are less tolerant to long waiting times and more prone to do premature actions, although they can achieve the same reward rate as adults. Thus, the aim of this project is to fully characterize how female and male rats of both age groups learn the rewarded task. We will evaluate if the prevalence of the impulsive actions correlates with other behavioral markers like locomotor activity, memory formation or decision making in the spontaneous exploration of a multiple-regions arena. Here we show pilot experiments of rats trained in the self-paced task and three other behavioral paradigms (open field, Y-maze and multivariate maze). Our preliminary results suggest that adolescent rats display more premature responses in the rewarded task, but this impulsivity is not related to increases in their locomotor activity or deficits in memory formation.

COGNITION

THE IMPACT OF SLEEP HYGIENE ON EMOTIONAL VARIABLES AND MEMORY PROCESSES IN PRISON INMATES

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Having a good sleep quality is essential for a healthy life. Lack or poor quality of sleep can negatively affect various brain functions such as emotional processing and memory acquisition and consolidation. In addition, prolonged sleep deprivation, as well as the deterioration of the sleep quality are correlated with depressed mood, anger, aggressive behavior and anxiety. The prison experience can be inherently stressful and lead to disturbed sleep patterns. In prison, the most common sleep disorder is insomnia. When left untreated, it can negatively affect daytime functioning and work productivity, and it can influence inmate adverse behavior such as exacerbating irritability or aggression. Improving sleep in prison offers the potential to positively impact several of these common risk factors for both staff and inmates. Thus, we propose a sleep hygiene treatment to improve sleep habits in the prison environment. Here, we will discuss preliminary data of the impact of one-month treatment of sleep hygiene in prison inmates on sleep quality, cognitive functions and emotional variables.

COGNITION

Characterization of age-related differences in the Multi-Variate Maze

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The multi-variate maze (MVM) is a test arena designed to evaluate explorative strategies. Animals can freely go through the whole arena which has different areas, some more related to risk-taking choices and others to the look for shelter. Several studies have shown that adolescent rats exhibit more risk-taking behaviors in contrast to adults. Moreover, in adolescents, it has been found that there are two opposite behavioral types: explorers -that have a high level of activity- and shelter seekers - that prefer to remain in sheltered areas of the maze-. The aim of this project is to study how subjects of different ages (adolescent, adults and older adults) behave in the MVM and to evaluate changes in their exploratory behavior in a second exposure to the MVM. Preliminary results shown here were obtained from training female and male Long Evans rats in the MVM. Besides, animals were also trained in two other behavioral paradigms (Open field and Y-maze) and their memory was tested 24 h after.

COGNITION

Structural plasticity of hippocampal dendritic spines following contextual fear memory reactivation

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The processes of learning and long-term memory formation have been associated with changes in synaptic efficacy, which, in turn, tightly correlate with morphological alterations in dendritic spines. This structural plasticity can occur on previously existing or newly formed spines, thus allowing new information to be encoded. But, what happens with spine morphology when a consolidated memory trace is reactivated? Using a contextual fear conditioning paradigm in mice, we studied long-term morphological changes associated to the process of reconsolidation, by assessing spine density and morphology in pyramidal neurons of the dorsal hippocampus CA1 area. For this purpose, we modulated memory reconsolidation by inhibiting nuclear factor κB (NF-κB), a transcription factor that not only has a well described role in synaptic plasticity and memory, but which is also an important regulator of activity-induced synaptogenesis. Measuring multiple morphological variables (total spine length, neck width, head diameter and head volume) and using a semi-automatic high-throughput methodology, we classified dendritic spines according to their maturity and related their structural plasticity with memory recall and restabilization.

COGNITION

Alcohol and energy drinks consumption in students of the University of Buenos Aires before and during the first year of COVID-19 lockdown

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Alcohol consumption (AC) can induce several negative consequences and is highly prevalent in university students (US). On the other hand, there are different factors that can promote an increase in AC, such as the intake of other beverages (e.g. energy drinks, ED) as well as social isolation (e.g. COVID-19 lockdown). Thus, the aim of this work was to evaluate the AC pattern and the potential impact of ED intake and lockdown in students from the University of Buenos Aires.
A sample of 1776 US completed an online survey that assessed the amount and frequency of alcohol and ED intake before and during the first year of COVID-19 pandemic.
Results showed that students' AC was highly prevalent both before and during the lockdown. In addition, it was observed that men consumed more alcohol than women. When comparing both time periods, the amount and frequency of AC decreased during lockdown. Moreover, few US consume ED, either alone or in combination with alcohol, and during lockdown its consumption decreased even more.
In conclusion, this study suggests that AC is highly prevalent in US, which is worrying given the negative consequences associated with it. Furthermore, factors such as ED intake did not promote higher AC, whereas lockdown decreased the consumption of this substance. Together, data suggest that although a decrease in social events seems to be an effective tool to avoid AC, people should be advised that solitary drinking might increase the risk of alcohol disorder

COGNITION

The role of sleep in episodic memory reconsolidation:Project and Preliminary Results

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Episodic memory is a subtype of declarative memory, defined as the ability to remember how, where and when past events occurred. Consolidated memories can be reactivated by a reminder of the original memory and can enter a new labile state, followed by a period of re-stabilization (reconsolidation). Sleep facilitates the consolidation of newly encoded memories and enhances the memory persistence 6 months after learning. Furthermore, it improves memory reconsolidation. It was demonstrated that a short nap accelerated memory re-stabilization of a list of nonsense syllable pairs, and facilitated the reconsolidation of the reactivated object-location memory, at short-term. Here, we aim to study the role of sleep on memory persistence of a neutral episodic memory through the reconsolidation process. For this, we developed an online paradigm of episodic neutral memories, to determine if it is possible to trigger the destabilization/re-stabilization processes under an online environment, using an interference task as an amnesic agent (Exp. 1). We also evaluated the effect of a home-nap after reactivation on memory persistence (Exp 2).

COGNITION

Collective memory shapes word usage across centuries

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Our everyday language is regulated by the cultural context, and also by cognitive features such as imitation and limited memory. Here we study how these factors interact to produce the dynamics of word usage. We capitalized on previous research showing that the occurrence frequency of words presents regular oscillations mounted on slowly drifting levels. We associated the drifting with the cultural environment and used it to drive a simple mathematical model that fits the data, capturing the dynamics of word usage in terms of imitation and memory. Fitting the dynamics of thousands of words across the last three centuries, we show that the oscillations are near to self-sustained and that the usage of a word at a given time is mainly influenced by its usage 7 years earlier. We found that words with similar usage form groups that represent keywords of historical periods. Finally, with the aid of our model, we show that the oscillatory coherence observed within these groups is provided by the cultural context driving the memory of the words. These results contribute to unravel how human cognition and historical forces interact to shape our use of language.

COGNITION

Metrics of Reading in Short Stories

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When reading, our brain constantly infers the structure of the sentence as it develops. Predicting upcoming words allows us to integrate information and to guide eye movements. Cloze-task experiments are used to estimate these predictions by asking a group of participants to complete the most likely word that follows a given context. Thus, collecting several responses per word.
A variety of measures could describe different aspects of this response distribution. The Predictability of a given word in a sentence, is estimated as the proportion of times that word is guessed over all guesses. Surprisal is the negative log of Predictability and assesses the unexpectedness of a word in its context. Entropy is a function of the probabilities of the different responses for a given context in the experiment.
Here, we present an analysis of a corpus of sentences drawn from short stories. An online cloze-task was conducted using isolated or contextualized sentences. Our previous work showed that Predictability is highly dependent on large contexts and is a strong predictor of eye movements and brain activity. Now, we explore how these metrics interact with other text variables (such as word-position, word-frequency, etc) and eye movement variables (fixation duration, regressions). Cloze-task-derived information-theoretical complexity metrics that connect theories of parsing and grammar to reading times and brain signals can help us understand various aspects of eye-movement control.

COGNITION

Deep understanding of the reactivation and re-stabilization process in memory reconsolidation in humans using an online platform.

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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. Moreover, it has been demonstrated that the reconsolidation process could be the tool to update memories in strength and content. This unique role opens new venues for therapeutic applications targeting dysfunctional memories.
The reconsolidation process, its functionality and its limiting conditions have been widely studied at a behavioural and pharmacological level, but little is known about whether this process could occur in an online experiment performance, and which measures would be relevant.
Here we aim to design a protocol targeting memory reactivation and the following re-stabilization stage to assess and characterize the dynamics of the process of an aversive and a neutral memory in humans. Subjects will be trained with face-name pairs and 24hs different groups will be compared, modifying the structure on Day 2. Thus, a cue-reminder (first syllable present) and a context-reminder (first syllable absent). The presence or not of specific instruction that the experiment cannot be completed (no mismatch), and different valence of the face expression stimuli for the reminder. On Day 3, memory retention in going to be assessed. We suggest that there are several boundary conditions for the reconsolidation process to occur. In particular, concerning the structure of th

COGNITION

Improvement of episodic memory retention by a memory reactivation intervention across the lifespan: from younger adults to amnesic patients.

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Mild Cognitive Impairment (MCI or Mild Neurocognitive Disorder) is an intermediate state between normal aging and dementia. MCI defines a condition of cognitive deficits associated with an objective memory impairment without compromising everyday functioning. In particular, episodic memory impairment is the hallmark of the amnesic MCI
subtype (aMCI).
Reconsolidation is a memory process by which reactivated long-term memories are transiently destabilize followed by its re-stabilization to update their strength or content. Re-exposure to specific learned cues has been shown to improve memory retention at long delays.
Here we tested the hypothesis that a Reactivation-based intervention would improve episodic memory performance in healthy adults and amnestic patients. We design a 3 day experiment, On Day 1, young adults, healthy older adults and aMCI patients learned face-name pairs and 24hs later either received a Reactivation-intervention or an Active Control. On Day 3, associative and item memory were assessed. Groups that underwent the Reactivation-based
intervention showed improved associative memory retention. Notably, amnestic patients benefited more from the intervention. These findings support memory reactivation as stabilization and strengthening mechanism irrespectively of age and cognitive status, and provides proof-of-concept evidence that Reactivation-based interventions could be implemented in the treatment and rehabilitation of populations with memory deficits.

COGNITION

THE ROLE OF DREAM CONTENT IN MEMORY PROCESSING DURING SLEEP: PRELIMINARY RESULTS

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After acquisition memories are in a labile state followed by a period of stabilization known as consolidation. This process is particularly favored by sleep, where the new information is spontaneously reactivated in the hippocampus, transferred and redistributed in neocortical networks facilitating long term consolidation. Also, during sleep, specifically during REM sleep, new memories are integrated into the stored information. From a neuroscientific perspective, dream content is proposed to be a consequence of the memory processes that occur during sleep. Thus, the incorporation of elements about the learned tasks during wakefulness in the content of a dream, can predict the performance of the task after sleep. Here, we studied whether dream content related to a new word learning task correlates with consolidation of new words and integration into the pre-existed semantic networks.

COGNITION

Acute LPS administration in the piriform cortex results in reduced sociability in mice.

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The autism spectrum disorder (ASD) is a group of pathologies characterized by social impairment and restricted and repetitive behaviors. Currently, the etiology of this disorder is not well understood. Our lab has validated a pharmacological model where mice prenatally exposed to Valproic Acid express ASD-related behaviors, along with higher glucose metabolism and increased cFos activity in the Piriform Cortex (PIR). Also, peripheral and brain inflammation have been associated with ASD. In this experiment, we aimed to understand whether an acute inflammatory insult in the PIR may alter the sociability of mice. First, we performed a three-chambered social interaction and novelty test (SI+SN) to assess the basal sociability levels of naive C57BL/6J mice. One week after, through stereotaxic surgery, we administered Lipopolysaccharide (LPS) bilaterally in the PIR, to elicit an acute inflammatory response. Twenty-four hours after surgery, we performed a new SI+SN test. We found that LPS completely abolished both the preference for the social side and for the social novelty. We aim to further characterize the effects of LPS on neuroinflammation, neuronal activity, and integrity of the PIR.

COGNITION

Searching for the hippocampal engram in a virtual discrimination task

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That memory persists after an experience suggests that an internal representation of this experience is stored in the brain and that later this representation can be reconstructed and used. This internal representation, known as the memory trace or engram, is constituted by subsets of neurons synchronously activated during learning. The dentate gyrus (DG) of the hippocampus participates in several mnemonic functions included the association of individual events with the background settings of an experience. Adult neurogenesis occurs in the DG producing different population of neurons at different stages of development during learning. We are conducting experiments training mice to perform a GO/NO GO discrimination task in a virtual reality environment. In head-fixed conditions, water restricted mice learn to drink water or not depending on the visual context presented in a virtual corridor. We show that animals reached to criterion within a few sessions and we analysed the development of distinct behavioural variables. We used cfostTA transgenic mice injected with AAV9-TRE-GFP in the DG to label activated neurons. By performing ex-vivo electrophysiological recordings, we aim to study the excitation/inhibition balance on activated and non-activated cells of expert animals. To further investigate the contribution of engram cells and adult-born neurons in this task, we are developing different transgenic mice lines to reversibly inactivate them using a DREADD approach.

COGNITION

Neonatal obesity: implications for memory impairment and neurosteroidogenesis dysregulation.

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The objective was to explore the importance of neonatal overnutrition on cognition and on the transcriptional control of steroidogenic enzymes. For that, rats were raised in small litters (4 pups/mother; SL), in which pups ingest larger amounts of milk and gain more body weight than rats raised in normal litters (10 pups/mother; NL). On PND21, half of the male rats were sacrificed (SL21 vs NL21; 8 pups/group) and the rest of males were maintained under standard conditions until PND90 (SL90 vs NL90; 14 rats/group). At PND90, animals were tested in locomotion activity (LA) and episodic-like memory (ELM). After two weeks, they were sacrificed and brains were microdissected. Using micropunch techniques, DG, CA1 and CA3 regions were isolated for mRNA and methylation quantification (results under analysis).
At PND21, SL21 animals had higher body and fat patches weights and greater levels of cholesterol, glucose and triglycerides, than NL21 rats. However, these metabolic differences were not observed at PND90. No differences were found in LA test, although SL90 rats reported a significantly increased of depositions than NL90 animals. During ELM, NL90 rats showed a very good test performance, while SL90 rats exhibited no clear preference during object exploration. Up to now, these results showed that neonatal obesity in males affects cognitive functions in adulthood, suggesting a long-lasting effect of nutritional experience during critical periods of early postnatal development.

COGNITION

Social behavior deficits following Serotonin 2A Receptor constitutive deletion

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Social behavior (SB) is defined as interactions among individuals that offer mutual benefits and comprise different actions. Deficits in SB are a hallmark of different psychiatric disorders, including autism spectrum disorders. Changes in 5-HT levels, as well as some activity of key molecules within the system have been associated with deficits in SB. Serotonin 2A receptors (5-HT2aR) are one of the main excitatory serotonergic receptors. Social deficits in humans were associated with 5-HT2aR hypofunction. Interestingly, 5-HT2aR agonists increase social interaction (SI) in humans and animal models suggesting that 5-HT2aR might modulate SB. We used genetically modified male and female mice (htr2a-/-) and their littermates' controls (htr2a+/+) to study the specific role of the receptor in SB. P90 or older animals were exposed to different behavioral paradigms. In the three-chambers SI test htr2a-/- male and female mice show decreased discrimination indexes compared with same sex htr2+/+ mice. Moreover, this deficit was rescued by the genetic restoration of the 5-HT2aR expression in the cortex suggesting a specific role of the receptor in this area. However, pharmacological manipulations in htr2+/+ adult mice before the SI test showed no effect suggesting that 5-HT2aR is not acutely recruited for SB. Taken together, these results suggest that 5-HT2aR has a role in SB and its involvement appears to be due to a developmental or chronic action.

COGNITION

Medial prefrontal cortex shows altered social encoding in a schizophrenia mouse model

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Schizophrenia (SZ) is a complex neuropsychiatric disorder that affects how a person thinks, feels, and behaves. Recent studies in rodents have been focused on social cognition impairments related to SZ to explain its poor social functioning. We have previously reported that restricted ablation of NMDAR in cortical GABAergic interneurons during early postnatal development results in SZ-like phenotypes in adulthood (KO). The medial prefrontal cortex (mPFC) controls many high cognitive functions reported impaired in SZ including aspects of social interactions. To date, little is known about how mPFC ensembles encode social information and how this representation might be altered in SZ. Here, we use an in-vivo electrophysiological approach to record putative pyramidal mPFC neurons activity in KO and control mice (Ctrl) while they perform a discrimination task on an enriched linear track with a novel social stimulus (adult male) and an inanimate object. In Ctrl, we identified units capable of encoding different aspects of the task, including neurons that discriminate social stimuli from the object and vice versa. The proportion of this type of units increased throughout the task in Ctrl. Conversely, KO displayed a higher proportion of non-coding units, suggesting an impaired representation of social stimuli at the population level. These results place an insight on how the mPFC neurons encode social information through a complex representation and how this may be disrupted in SZ.

COGNITION

Emotional word recognition on a non-native language: Preliminary results using signal detection theory

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Word processing differences between people's first (L1) and second (L2) language are a developing field in cognitive neuroscience research. Previous research shows that item recognition and recall is modulated by the emotional content of the stimuli, since emotional stimuli are remembered better and recognized faster than neutral words. The aim of this study was to assess emotional word recognition on L1 vs L2, and to investigate the effect of a visual feedback (VF) on recognition sensitivity. Fifty-eight bilingual volunteers performed a lexical decision task in which they had to decide whether a given string was a word (positive, neutral, or negative) or not, either on L1 or L2. Participants were split into four groups: L1/VF ((n = 14) and L2/VF (n = 15) performed the task with VF, while L1/NVF (n = 15) and L2/NVF (n = 14) performed the task without VF. Results indicated that participants showed higher sensitivity (d') scores for L1 than L2, benefiting from the VF. Likewise, L1 groups had shorter response times. Overall, positive words were recognized faster than neutral and negative words. However, bias index (C) analyses showed higher tendency to answer "word" for positive words in L2 but not in L1; these groups showed higher tendency to answer "word" only for negative stimuli. Therefore, even though word recognition is more efficient in L1, bilingual people show different strategies for processing stimuli in L1 and L2.

COGNITION

Memory updating and reconsolidation: Role of dopaminergic and noradrenergic systems from a behavioral tagging perspective

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The behavioral tagging (BT) hypothesis proposes that lasting memories require the synthesis of plasticity-related proteins (PRPs) and the setting of a learning tag. The latter will capture the PRPs to stabilize the memory trace. We have previously shown that memory reconsolidation also fits this model. Here, we show that the dopaminergic and noradrenergic systems specifically regulate the synthesis of PRPs in the BT process during memory reconsolidation.
Using a spatial object recognition task (SOR) in rats, we show that antagonizing the hippocampal D1/D5-dopaminergic, or the β-adrenergic receptors, during memory reactivation impaired its reconsolidation. However, this requirement was overcome by the exploration of a novel open field (NOF) within a critical time window around the reactivation session. This phenomenon was dependent on PRPs synthesis triggered by the novel experience. Moreover, behavioral novelty could be replaced by the electric stimulation of the VTA or the locus coeruleus.
These neuromodulator systems also play a central role in adding new information to the memory trace during its reconsolidation. Again, their requirement upon memory reactivation could be overcome by the previous exploration of a NOF that enables PRPs synthesis.
Taken together, our results position these neuromodulator systems within the reconsolidation BT process as key regulators of PRPs synthesis, crucial for trace stabilization of the original and the newly acquired information.

COGNITION

Cognitive mechanisms of the persistence of fake news about COVID-19

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Whether people believe fake news because they want to or because we just don't focus enough on the veracity of the consumed piece of information, we know that beliefs about COVID-19 correlate with compliance to recommended public health behaviours, thus affecting the sanitary state of a region. This is one of the first exploratory studies in Argentina to study it. The participants (N = 2235) answered a survey with demographic data, information consumption habits and the last presidential vote cast, then 9 false news and 9 real news related to COVID were presented in random order with questions about familiarity, emotional response, willingness to share and truthfulness of each stimulus. Upon completion, the participants had to complete the Cognitive Reflection Test as a measure of propensity to engage in a detained and analytical mode of thinking as well as two proxies of metacognition (self-assessment of performance) and conspiratorial thinking. Some of the preliminary results of this study seem to locally confirm hypotheses present in the literature about the effect of familiarity on accuracy when evaluating the veracity of the news or an inverse correlation between age and performance. While other results revive the discussion about the possible link between the vote cast, the political content of the stimuli and the accuracy of the subjects, as well as show an inverse correlation between CRT and confidence that official bodies provide true information about the pandemic.

COGNITION

Dentate gyrus role in spatial learning of alternative paths to a unique goal

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Every day, mammals need to plan and execute efficient actions for survival. We believe the dentate gyrus (DG) of the hippocampus, known to be involved in pattern separation, is critical to distinguish between similar alternative routes to the same goal. We set up a crossword maze in which mice learnt two spatial routes in an alternative manner to reach a unique reward position during a 1-h training session. Chemogenetic inhibition of dorsal hilar neurons using hM4Di induced a poor performance during the learning of one of the routes after mice had found the reward using the alternative path in the previous trial. We then investigated if the dorsal DG was needed for the rapid discrimination between alternative routes to the reward, or whether it also contributed to the learning performance. We thus broadened the expression of hM4Di to the majority of dorsal DG neurons (hilus + granule layer) to get a complete manipulation. Interestingly, inhibition of the dorsal DG only impaired the pursuit of reward in the second learned route, once mice had reached the goal location using the alternative path. All subjects managed to learn the first path in which they have found the reward, regardless of its difficulty. Our results suggest that the dorsal DG may not be important for learning per se of the spatial task. Instead, we propose that the DG may enhance the resolution and identification of similar spatio-temporal information to reach a goal using an optimal strategy.

COGNITION

Social deficits in adult mice subjected to postnatal ablation of the NMDA receptor in GABAergic interneurons.

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Schizophrenia is a chronic neurodevelopmental disorder characterized by a complex syndrome that includes psychotic, affective and cognitive features. Our team has previously developed a murine model based on the postnatal ablation of the NR1 subunit of the NMDA receptor in cortical and hippocampal GABAergic interneurons. This approach has proven valuable in reproducing pathophysiological aspects of schizophrenia along with a series of behavioral deficits relevant to its symptomatology. While altered social behaviors have been previously reported in this model, a clear depiction of the affected social domains has not been achieved, precluding the comparison with symptoms of schizophrenia. In this study, we focused on social dominance and aggressive behaviors. In the resident-intruder test, both an increase in the latency to the first attack and a reduction in the number of attacks were detected in knockout animals. Spontaneous dyadic interactions with younger mice and an adaptation of the three-chamber test were also conducted to search for social abnormalities. Determining the face validity of an animal model is crucial to further our understanding of human neuropsychiatric disorders and to develop novel therapeutics.

COGNITION

Performance in Lineups during the Covid-19 pandemic. Influence of lock-down side effects

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The covid 19 pandemic has caused major disruptions in people's lives around the globe. Sleep habits and emotional balance have been disturbed in a way that could be comparable to the havoc caused by a deep personal crisis or a traumatic experience. This unfortunate situation provides a useful context in which to study the impact of these imbalances on cognitive processes. In particular, the field of eyewitness science could benefit from these conditions, since they are also often present in crime victims, but can only be generated in the laboratory up to a certain ethical and practical limit.
Here, we perform simple and repeated lineups with witnesses of mock-crime, considering the conditions related to the COVID-19 pandemic, which to some extent allow emulating the deterioration in general well-being that often afflicts crime victims. For this, 72 participants completed symptomatology scales, and watched a video portraying a staged violent episode. Subsequently, they gave testimony and participated in two lineups, in which we manipulated the presence / absence of the perpetrator, to recreate critical scenarios for the appearance of false recognitions.
We found an increase in recognition errors in those individuals who did not have access to the perpetrator during the Initial Lineup. Additionally, the high levels of anxiety and bad quality of sleep developed during the Covid-19 Pandemic adversely affected the ability to witness and accurately recognize a perpetrator.

COGNITION

K-Complex localization and classification algorithm

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K-complexes (KC) are events present in non-rapid eye movement (non-REM) sleep, which have cellular dynamics similar to slow waves and three distinguishing components: initial positive wave (P200), posterior negative wave (N500) and final positive wave (P900). They can be generated spontaneously in cortical networks but can also be induced by cortical, thalamic or sensory stimulation.

Sleep plays a fundamental role in memory consolidation, favoring the transfer of new information from the hippocampus to the neocortex and its cortico-cortical redistribution. There are no studies that directly link KCs with memory processes; however, reactivations during sleep, with cues associated with previously acquired information, induce evoked potentials similar to KCs. Therefore, KCs could be participating in the memory consolidation process during sleep and they are not being taken into account as a possible facilitating event of the hippocampal-cortical dialogue. Consequently, in order to study these events more deeply, we propose a Machine Learning based algorithm.

COGNITION

The role of 20-min naps on declarative memory persistence

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It has been demonstrated in different species and types of memories that a night of sleep improves memory consolidation of recent acquired information. Furthermore, even a 6min-nap benefits memory storage. It has been proposed that neocortical slow oscillations (0.5-1 Hz) during Non Rapid Eye Movement sleep (NREM), orchestrate the hippocampal-cortical dialog, promoting memory reactivation in the hippocampus through the hippocampal sharp wave ripples, together with the thalamocortical spindles, which participate in the induction of durable plastic changes in the neocortex.
Recently, sleep has been proposed as a tool to improve education. However, to implement that in a school setting, more research has to be conducted studying the effects of short naps in memory processes as well as the mechanisms involved. Here, we studied the effect of a short nap on memory persistence. Participants learned 5 pairs of nonsense syllables on Day 1 and slept for 18.7 min while a polysomnography was performed, or they remained awake. They were finally tested on Day 8. We found that sleeping 18.7 min after learning the task improves memory persistence and that slow oscillations are involved in memory consolidation of the syllable pairs. Moreover, as NREM stage 2 is the predominant sleep stage scored in these short naps, almost all slow oscillations detected correspond to K-complexes. Thus, we discuss the possible role of these complexes in the hippocampal-cortical dialog.

COGNITION

Improving offline consolidation by odor cuing memory reactivations in a school setting: Preliminary results

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During sleep, recently acquired memories are spontaneously reactivated in the hippocampus, transferred and redistributed to neocortical networks favoring memory consolidation and persistence. Furthermore, these reactivations can be induced by presenting a cue during sleep, previously associated to the learned material. Up to now, these reactivations have been induced in the Lab under controlled environments showing memory improvement after reactivation. However, it has been recently shown that the same effects could be obtained at home with the experimental subjects auto-administering the cues during sleep. Thus, this approach results particularly interesting for improving consolidation in a school setting. Here, we will discuss preliminary data of odor reactivation during sleep previously linked to a history lecture in the classroom and its impact on memory persistence.

COGNITION

Visuospatial perception in subjects with out-body-experiences

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Visual imagery typically refers to the voluntary creation of the conscious visual experience of an object or scene in its absence, solely in the mind. There are individuals who have no experience of imagery at all –their minds are completely blind: aphantasia. Hyperphantasia is at the other end of the imagery spectrum: strong and often photo-like imagery. One of the key limitations to studying visual imagery has been its internal private and subjective nature. An intrinsic characteristic of the imagery experience is its degree of vividness, the clarity and richness of the mental representation. The most commonly used questionnaire is the vividness of visual imagery questionnaire (VVIQ). We developed a novel way to study visual imagination through an auditory guided visualization exercise. After completing the exercise, participants solve tasks and questionnaires related to their visuospatial performance, episodic memory, and quality of the experience, correlated to their visualization skills as measured by the VVIQ. A handful of individuals from sleep paralysis have out-of-body experiences (OBE, the experience in which the observer perceives the world from a point of view outside of his physical body), described as "incredibly vivid and having the qualities of veridical perception". We hypothesized that participants with frequent OBEs will have a distinct visual imagery strategy (and experience) not explained by their VVIQ score. We present preliminary results of this study.

COGNITION

Cognitive training personalization: an AI approach

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Executive functions (EF) are a class of processes critical for purposeful goal-directed behavior. Cognitive training (i.e. the adequate stimulation of EF) has been studied and applied for the last 25 years in hugely diverse backgrounds. In spite of the accumulated evidence of its positive impact in cognition, there are still reports in the literature that claim that the potential benefits of training are not generalizable. Recently, research considers individual differences as one of the possible causes of these inconsistencies. Is it possible to build one training protocol that benefits everyone? Or is it time to stop considering individual differences as inevitable experimental noise and, instead, use them as information that can guide us towards finding the best possible strategy for each person?
In this study we use Machine Learning algorithms to identify and describe possible subgroups of individuals that will (or will not) benefit from a certain stimulation. The algorithms were built using data from a cognitive training intervention (N=73 6 y.o.) run with a set of computerized games aimed at training and measuring EF (www.matemarote.org.ar).
We present a Nearest Neighbors classifier that successfully predicts whether a subject will benefit or not from a fixed training approach based on his/her performance in previous cognitive tests. In the long term these algorithms will allow us to individualize training protocols in order to maximize the stimulation for each child.

COGNITION

Serotonin receptors 2A in the rat mPFC are necessary for Retrieval Induced Forgetting

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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 and selective 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). Humans and rats share the fundamental features of RIF: competition-dependent, cue-independent, and reliant on the prefrontal cortex. This work aims to explore if and how the serotonergic system participates in RIF. Precisely, we first used an antagonist of the serotonin receptor 2A (5-HT2AR), then specific inhibitors for members of the βarr2 signaling pathway, and finally an agonist of the 5-HT2AR in the medial prefrontal cortex. We found that a 5-HT2AR antagonist and a PI3K inhibitor, which is part of the Barr2 pathway impaired RIF but did not affect memory in other ways. Moreover, injection of a 5-HT2AR agonist promoted RIF in animals that would not normally forget. In summary, 5-HT2AR signaling in the rat prefrontal cortex is necessary for the occurrence of RIF and is partially reliant on the activation of the Barr2 pathway.

COGNITION

Performance of ventromedial patients on the Iowa Gambling Task

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The Iowa Gambling Task (IGT; Bechara et al. 1994) is commonly associated with research on decision making under uncertainty. It is a task, developed within the framework of the Somatic Marker Hypothesis (HMS), which simulates decision-making in real life. Initial results show that patients with ventromedial cortex (VM) damage have poor performance on IGT despite retaining their reasoning abilities. This leads to the hypothesis that such patients have a deficiency in the somatic affective signal (somatic marker) that is critical to guide their behavior advantageously, regardless of conscious awareness of the task. Recent research questions the validity and reliability of the IGT on the subsequent analysis of the evidence in healthy participants, arguing that 1) they do not exhibit a predominant choice of advantageous options and 2) their behavior is widely heterogeneous. However, this analysis is performed outside the context of comparison with MV patients. Around this debate, the objective of this work has been to carry out a systematic review on the performance of VM patients in IGT. Our results show a significant difference between the performance of healthy subjects and VM, highlighting the advantageous behavior of healthy subjects compared to the pathological group. In effect, we question the interpretation of the results of healthy participants and the consequent criticisms of HMS.

DEVELOPMENT

Consequences of diet quality in early life on brain development and behavior: a meta-analysis

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Malnutrition comprises both undernutrition and overweight/obesity, and it is suffered by about a quarter of the worldwide population. The long-term consequences of undernutrition on body growth and brain development have been largely studied. Although less studied, recent research reports that also overweight can have consequences on brain development. Most interestingly, changes in lifestyle and diet have resulted in a new phenomenon, known as the double burden of malnutrition (DBM). Among DBM phenomena, children can suffer from undernutrition in the earlier years of development, and experience overweight and even obesity later in childhood. The consequences of these alterations in body mass and metabolism have not been extensively analyzed, and their effect on brain development is unknown.

Here, we performed a meta-analysis, searching for the current knowledge of the consequences of undernutrition and obesity on brain development, and their effects on brain function, especially on animal behavior. We identified a variety of protocols to model both undernutrition and obesity in rodents and analyzed the strengths and weaknesses of each model. Although no model completely recapitulates de particularities of human malnutrition, we conclude that animal studies can shed light on unexpected consequences of early alimentary behavior on brain health

DEVELOPMENT

The effect of chronic maternal stress on the neurocognitive outcome of two years old toddlers.

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Children affected by maternal stress before, during and after pregnancy may program their physiological responses later in life. In this study, we assessed the neurocognitive outcome of a cohort of toddlers exposed to prenatal stress (PS). In a prospective case-control study, German speaking pregnant women (~34 weeks of gestation) were screened for stress exposure using Cohen Perceived Stress Scale (PSS) and classified into stressed (SG, PSS-10≥19, n= 40) and control groups (CG, PSS-10<19, n=44), matched 1:1 for parity, maternal and gestational age. Two years after delivery, infants' cognitive, language and motor development were assessed by Bayley Scale III of Infant Development (BSID). Cognitive and motor areas showed no significant variation between SG and CG toddlers even when accounting for sex. However, language composite scores showed a significant decrease in SG toddlers irrespective of sex and language spoken at home. When day care center attendance (DCA) was accounted for, this effect disappeared. PS affects the toddler´s language development in both sexes, regardless the language spoken at home. DCA seems to protect for this neurodevelopmental delay. These results confirm the importance of early stimulation through social interaction for reversion of language delays in toddlers exposed to PS.

DEVELOPMENT

Neural stem cells temporal dynamic in the pallium of adult zebrafish

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Adult neurogenesis is the process of generating new neurons from neural stem cells (NSCs) in the adult brain, a type of plasticity highly conserved through evolution. Zebrafish exhibits abundant adult neurogenesis in their pallial sub-regions. Of particular interest are the dorsomedial (Dm) and dorsolateral (Dl) pallium, because these structures share homology with the basolateral amygdala and the mammalian hippocampus, respectively.
To explore the NSCs differentiation, we labeled a cohort of dividing NSCs with the thymidine analog EdU to study their differentiation process over time. We found that the distribution of EdU+ cells decreases along the rostrocaudal axis in Dm, whereas the opposite pattern occurs in Dl. Furthermore, we found that the number of EdU+ cells decreases in all regions after eight weeks, indicating cellular death. Interestingly, we found that Dm EdU labeled-NSCs continue proliferating throughout the eight weeks period, whereas Dl NSCs decrease their proliferation two weeks after EdU labeling. These results reveal the temporal dynamics where NSCs divide to preserve the stem cell reservoir, whereas cellular death contributes to tissue homeostasis. At this moment we are evaluating the fate that these NSCs adopt after differentiation.

DEVELOPMENT

Epigenome wide- association study of maternal stress in newborn saliva: FELICITy Study.

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Maternal stress during pregnancy can program the infant's lifelong trajectory and physiological stress response systems. We hypothesize that the stress-induced alterations can be gauged by the infant epigenetic biomarkers, which can be employed for early detection and follow up of affected children. Pregnant women were screened for stress exposure using Cohen Perceived Stress Scale (PSS-10) and were classified into stressed (SG, PSS-10 ≥ 19, n= 79) and control group (CG, PSS-10 <19, n=85) matched 1:1 for parity, maternal and gestational age. Prenatal Distress Questionnaire (PDQ) was also administered to assess specific pregnancy worries. Upon delivery, maternal hair strands were collected for cortisol measurements and newborn's saliva samples were collected. DNA was extracted from saliva samples (n=114) and DNA methylation was measured using EPIC Bead-Chip array (850k CpG sites). To identify associations between PDQ/Cortisol and methylation, linear regression models adjusting for confounders were run in R. We found epigenome-wide significant associations for five CpG sites in association with stress phenotypes (PDQ and cortisol) at FDR < 5%. Annotated genes were found to be enriched for development and growth in hippocampus signaling pathway, organelle biosynthesis, and metabolism of proteins, cell proliferation and bone development. We report novel associations between DNA methylation patterns in newborn saliva and maternal stress that might be harnessed as early biomarkers

DEVELOPMENT

Gradients of EphA3, GDNF and BDNF have chemo-attractant effects on retinal ganglion cell axons

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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. GDNF and BDNF stimulates RGC axon growth.
Our purpose was to study the individual and combinatorial effects of EphA3, GDNF and BDNF on RGC axon guidance.
We cultured chicken embryo nasal retinal explants and dissociated RGCs and exposed them to control conditions, to EphA3 ectodomain (aggregated EphA3-Fc), GDNF, BDNF or to EphA3-Fc plus GDNF or EphA3-Fc plus BDNF to evaluate their effects on axon guidance.
We developed the technique of Stripe assay using retinal explants. Nasal RGCs axons preferentially grow on a substrate with EphA3 instead of a permissive substrate of laminin. This axonal preference is not modified with the addition of GDNF or BDNF.
In order to evaluate the participation of soluble gradients of EphA3, GDNF and BDNF on the axonal guidance of nasal RGCs, we developed a chemotaxis test using the Dunn's chamber.
RGC axons change their directions of growth toward gradients of EphA3, GDNF, BDNF and their combinations. Furthermore, EphA3-Fc plus GDNF together present the highest effects in comparison to the effects produced by any of them alone.
This demonstrates that gradients of EphA3, GDNF, BDNF and their combinations have chemo-attractant effects on nasal RGC axons, suggesting that the combination of EphA3 and GDNF present synergistic effects.

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DISORDERS OF THE NERVOUS SYSTEM

Enduring morphological alterations in microglia of Nucleus Accumbens core, but not shell, underpin chronic restraint stress-induced addictive behaviors

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It is well documented that stress-experienced rats evidence an enduring sensitized response to cocaine and facilitation of cocaine self-administration (SA), which were associated to a key involvement of Nucleus Accumbens (NA) core, but not shell. Studies suggest that neuroinflammatory processes may represent a critical issue in stress-induced drug abuse liability. For instance, repeated exposure to stress and addictive drugs may disrupt the microglial phenotype accompanied by structural remodeling. Since the morphometric features of microglia have not yet been described in animal models of chronic stress-induced addictive behaviors, we performed a comparative morphometric analysis of microglia in the NA, core and shell, using a systemic treatment with minocycline, a potent inhibitor of microglia activation. Thus, male rats were restrained 2h daily for a week (day 1-7). From day 16 until completing the experimental protocol, animals received minocycline or vehicle. On day 21, behavioral and immunohistochemical studies were performed. Our results showed that: 1) minocycline prevented chronic stress-induced cocaine sensitization as well as facilitation of cocaine SA, and 2) stress-induced a hyper-ramified microglial profile in the NAcore, but not shell, which was restored by minocycline. These results strongly suggest that NAcore microglia critically contribute to the biological mechanisms underpinning the comorbidity between stress and substance use disorders.

DISORDERS OF THE NERVOUS SYSTEM

Yerba mate (Ilex paraguariensis) in a Drosophila model of Parkinson´s disease

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Parkinson's disease (PD) is the second neurodegenerative disorder in prevalence. Its origin is unknown, but its pathophysiological characteristic is the progressive degeneration of dopamine-releasing neurons of the Substantia nigra.A clinical study conducted in Argentina revealed that the consumption of yerba mate (YM) has an inverse association with the risk of developing PD (Gatto, 2015), and we found that YM extract induces a strong neuroprotective effect on dopaminergic neurons in vitro (Bernardi, 2019). Given these results, we hypothesized that the YM extract would also protect neurons from the deleterious effects caused by the expression of human alpha synuclein (aSyn) in a widely used Drosophila melanogaster model of PD. To reach this goal, we have set up the administration of YM to these fly disease model and produced preliminary behavioral and molecular data. Preliminary experiments using GRASP (GFP Reconstitution Across Synaptic Partners) technique, showed an increased GFP signal (a reporter of synaptic connections) between circadian and dopaminergic neurons in aged wild-type flies treated with YM, suggesting more connectivity in treated flies. Unfortunately, these experiments were interrupted by the pandemic when we were going to replicate this study in the aSyn flies. Our preliminary results show that YM administration improves motor coordination in PD flies and could also maintain synapses in wild-type flies; perhaps an indication of healthier neuronal circuits?

DISORDERS OF THE NERVOUS SYSTEM

General anxiety and depression are associated with the physical activity and social interaction levels: Study in Argentinean university students during the COVID-19 outbreak.

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Due to the coronavirus disease 2019 (COVID-19), the planet is going through a historical time of exceptional concern and uncertainty, which impacts people's mental health. Here, we explored the levels of depression and Generalized Anxiety Disorder (GAD) and their relation with the degree of physical activity and social interaction during the pandemic.
We performed a structured survey containing the PHQ-9 and GAD-7 tests to evaluate
depressive symptoms and GAD levels. We also asked about weekly physical activity and the level of social interaction. We surveyed two groups of University students in the Buenos Aires Metropolitan Area: an internal group from the Instituto Tecnológico de Buenos Aires, and an external group of students from multiple universities. The survey was conducted in late October/early-November 2020, after a peak of contagions. Some of the participants were surveyed again in January 2021, during academic holidays and after a valley of contagion, for longitudinal analysis
Our data show that men and women of both groups exhibited a significant positive linear
correlation between depression and GAD levels. Moreover, low levels of depression and anxiety were associated with performing physical activity for more than two days a week and to longer periods of social interaction. Finally, the second survey revealed a decrease of the symptoms.

DISORDERS OF THE NERVOUS SYSTEM

Cognitive impairment and anxiety-like behavior characterization in a rat experimental model of dopaminergic depletion induced by 6-OHDA neurotoxicity

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Parkinson's disease results from a progressive dopaminergic neuronal loss, characterized by multiple, motor and non-motor symptoms. Currently its diagnosis is based on motor deficits, but a variety of previous and coexisting non-motor symptoms result from dysfunction of interconnected systems. We aimed to determine, in a rat model of neurotoxicity, the progression of working memory deficits and anxiety-like behavior and its correlation with cellular changes. Animals were injected with 6OHDA in dorsal lateral striatum (DLS) or with control solution (experimental or control groups, respectively). Independent groups of rats were tested only once in a behavioral task after 2 and 3 weeks (Y-maze, elevated plus maze and locomotor activity test). Then, they were perfused and IHC processed for neurons, astrocytes and microglia cell markers in the substantia nigra, DLS, dorsal hippocampus, prefrontal cortex and ventral tegmental area. Two weeks post lesion there were no significant changes in any behavioral task. We observed working memory and anxiety-like behavior impairments in 6OHDA rats after 3 weeks of neurodegeneration, without motor alterations. These results could be associated with a partial lesion of the nigrostriatal DA system and glial cells number changes observed in brain regions. We concluded that a single bilateral infusion of 6OHDA induced non-motor alterations that preceded locomotor deficits in the employed dopamine depleted animal model.

DISORDERS OF THE NERVOUS SYSTEM

Consequences of light exposure on retinal health

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The effects of excessive artificial light, a phenomenon known as light pollution, has direct consequences on retinal health. Constant exposure of light promoted by light pollution may produce retinal degeneration (RD) as a consequence of photoreceptors cells death. It is noteworthy that modern life has extended the environmental illumination with artificial LED lights for several hours to prolong the work schedule, night shift and use of tablets, cellular phones and tv screens for longer times and causing severe effects on the eye. We have characterized the behavior of the neural and glial retina in a pathologic context of light pollution.

DISORDERS OF THE NERVOUS SYSTEM

Lack of Cdk5 activity is involved on Dopamine Transporter expression and function: Evidences from an animal model of Attention-Deficit Hyperactivity Disorder

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Attention deficit/Hyperactivity disorder (ADHD) is one of the most diagnosed psychiatric disorders. The core symptoms include hyperactivity, impulsiveness and inattention. The main pharmacological treatment consists of psychostimulant drugs affecting Dopamine Transporter (DAT) function. We have shown that mice lacking p35 (p35KO) which have reduced Cdk5 activity, present key hallmarks resembling those described in animal models of ADHD. The p35KO mouse displays spontaneous hyperactivity and shows a calming effect of psychostimulant treatment. Besides, Dopamine (DA) neurotransmission is altered in these mice as they have an increased DA content with a low DA turnover. This led us to hypothesize that the lack of Cdk5 activity affects DAT expression and/or function. We performed biochemical assays, cell-based approaches, quantitative fluorescence analysis and functional studies that allowed us to demonstrate that p35KO mice exhibit decreased DA uptake and reduced cell surface DAT expression in striatum. These findings are supported by in vitro observations in which the inhibition of Cdk5 in N2a cells induced a significant increase in constitutive DAT endocytosis with a concomitant increase in DAT localization to recycling endosomes. These data provide evidences regarding the role of Cdk5/p35 in DAT expression and function, thus contributing to the knowledge of DA neurotransmission physiology and also providing therapeutic options for the treatment of DA pathologies such as ADHD.

DISORDERS OF THE NERVOUS SYSTEM

Cerebral cortical activity in migraine: a LORETA analysis.

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PERSPECTIVES: to study the functional state of the retina in animals exposed to constant light and them recovery by L:D cycle; and the glutamatergic neurotransmission relationship to this RD.

DISORDERS OF THE NERVOUS SYSTEM

Assessing degeneration of corticospinal tracts in a TDP-43 transgenic mouse model of ALS/FTD: application of 3D reconstruction in cleared tissue.

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The neurodegenerative diseases amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) represent two ends of one spectrum disorder, termed ALS/FTD. These incurable pathologies are now classified as “TDP-43 proteinopathies”, since mislocalization and aggregation of the nuclear protein TDP-43 are hallmark features of most cases. A main feature of ALS/FTD is degeneration of the corticospinal tract (CST), composed of axons of upper motor neurons, being the main motor pathway involved in voluntary movement. We are using a novel approach, combining a cost-effective unsectioned brain/spinal cord clearing technique, fluoroRuby staining, one-photon confocal microscopy and 3D reconstruction to study the morphological changes in the CST of TDP-43 transgenic (TG) mice. We have previously shown in mice that inducible overexpression of a cytoplasmic (ΔNLS) form of TDP-43 in forebrain neurons evokes neuropathological and behavioural changes that recapitulate several features of TDP-43 proteinopathies. Our preliminary results showed proper and consistent tracer delivery, with similar number of labelled cortical neurons in control and TG mice. TDP-43-ΔNLS expression decreased the length of cortical apical processes and the number of cervical axons. Remarkably, suppression of TG expression (displaying reversible motor phenotypes) led to an increase in cervical axonal branching. These studies will help to elucidate the mechanisms underlying the motor phenotypes in ALS/FTD.

DISORDERS OF THE NERVOUS SYSTEM

Neonatal exposure to 17beta-estradiol results on impairment in social habituation in adult females prenatally exposed to valproic acid

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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 to 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 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, due to the early exposure to gonadal hormones, is necessary for prenatal VPA exposure to affect autism-related behaviors.

To test this hypothesis, we studied the effect of neonatal exposure to 17β-estradiol benzoate (E2) in female mice of the VPA model. We carried out an comprehensive behavioral analysis of these animals. In the habituation and novelty recognition task, we observed that only VPA-E2 females failed to habituate to the stimulus mouse. We also found that E2 exposure results in reduced immobility in the forced swim test and a lower latency to approach the food in the novelty suppressed feeding.

E2 treatment was sufficient to alter the normal development of secondary sex characteristics, as ovaries of E2 females weighed less than those of OIL females.

Further studies of the VPA-E2 mice could help us identify possible biological mechanisms underlying the behavioral effects of both VPA and masculinization.

DISORDERS OF THE NERVOUS SYSTEM

Long- Term Behavioral Alterations in mice that were Transiently Depleted of 5-HT During Embryogenesis.

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Introduction: Serotonin (5-HT) is an indoleamine molecule that functions as a neurotransmitter. Dysregulation of 5-HT transmission in the CNS is reported to be related to different psychiatric disorders. A key component of the system is the serotonin transporter (SERT), regulating serotonin availability in the synaptic cleft through reuptake of serotonin. The aim of the experiment was to analyze long-term effects of transient 5-HT depletion on social behavior, anxiety and compulsive behavior. Methods: Mothers has Dams were treated with 200 mg/kg/day of PCPA, vehicle (saline) or were undisturbed at gestational days (E) 12-14. During postanatal days (P) 7, 21 and 42 frequency and duration of ultrasonic vocalizations (USV). At P64 all animals were subjected to 30 min of marble burying test (MB). 24 h after MB, animals underwent 5 min of light/dark box test (LDB). 48 h after last treatment, dissecionsdissections of mPFC and Raphe were obtain in order to analyze mRNA expression of SERT Results: Frequencies of USVs were altered in adolescence. These alterations are not observed during infancy or at weaning. Animals treated with PCPA did not displayed an anxiety-like phenotype, with a downregulation of SERT expression in mPFC. Conclusions: Transient prenatal depletion alters social and anxiety-like behavior during adolescence and young adulthood. This could be linked to a downregulation of SERT in mPFC, that could lead, in turn, to an overexpression of 5-HT in this area, a symptom

DISORDERS OF THE NERVOUS SYSTEM

D5 dopamine receptor expression in striatal cholinergic interneurons after nigrostriatal degeneration and L-dopa treatment

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Striatal cholinergic interneurons (SCIN) have been implicated in the motor deficits of Parkinson's disease (PD) and also in L-dopa-induced dyskinesias.
In previous work, we reported a reduction in a potassium membrane current containing Kv1.3 subunits that mediates SCIN hyperexcitability in a mouse model of PD. L-dopa treatment not only did not revert this effect, but instead turned SCIN even more excitable and further reduced Kv1.3 current. This was not due to a decrease in cell surface localization of Kv1.3.
SCIN express D5 dopamine receptors (D5R) that modulate Kv1.3 SCIN currents and may mediate the hyperexcitability produced by L-dopa treatment. As these effects persist after L-dopa has worn off and D5R stimulation ceases, we propose that increased ligand-independent activity (L-IA) of D5R contributes to negative regulation of Kv1.3 in dyskinetic mice.
As increased L-IA can derive from increased expression of D5R, here we address whether D5R are differentially expressed in SCIN from control, parkinsonian and dyskinetic mice. For this, we performed immunohistochemistry labeling of D5R in brain sections from mice that express a red fluorescent protein in all cholinergic neurons and acquired images from the dorsolateral striatum. Preliminary results from the quantification of D5R label in SCIN somata show higher D5R levels in dyskinetic than parkinsonian mice. These results suggest that targeting D5R in SCIN could provide new anti-dyskinetic therapies.

DISORDERS OF THE NERVOUS SYSTEM

Comorbid Impulsivity and Epilepsy

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Purpose: Psychiatric comorbidity in patients with resistant epilepsy is very common and often develop post-surgical psychiatric disorders. Impulsivity may be present and deepen the disorder's severity. We analyze the post-surgical evolution and degree of impulsivity in these patients.
Method: We included patients operated and assessed with a neurological, neuropsychological, psychiatric assessments, vEEG, MRI. One year after surgery, Barratt Impulsivity Scale was administered to the patients' follow-up. Student's t-test and chi-square were performed.
Result: 38 patients were included (21 women). 24 patients (63%) presented pre-surgical psychiatric disorders, either current or past. A pre-surgical psychiatric diagnosis was associated with the development of post-surgical psychiatric disorders. Lower GAF scores were correlated with higher impulsivity scores. A post-surgical diagnosis was associated with higher motor and total impulsivity scores. The evolution of postsurgical epileptic seizures, according to the Engel classification: Engel I (58%), II (21%), III, IV (21%). Worse postsurgical outcomes were associated with higher nonplanning impulsivity score.
Conclusions: Post-surgical psychiatric comorbidities are more frequent in epileptic patients with a psychiatric history, being depression the most frequently diagnosed. Additionally, de novo postsurgical psychiatric disorders are infrequent. Nonplanning is strongly correlated with seizure outcome following surgery.

DISORDERS OF THE NERVOUS SYSTEM

STUDY OF THE LRP1/α 2 M SYSTEM DURING CHOROIDAL NEOVASCULARIZATION.

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Age-related macular degeneration (AMD) in its Choroidal neovascularization (CNV) stage, where the growing neovessels invade the retina inducing photoreceptor degeneration, is the leading cause of vision loss among adults. Our lab has previously demonstrated that α2M and its receptor, LRP1, participate during retinal NV. Moreover, other authors propose LRP1 as a regulator of inflammatory responses. In the present study, we characterize the neovascular process and the pro-inflammatory profile, emphasizing on the level and localization of the α2M/LRP1 system in CNV. Experimentally, C57BL/6 adult mice were treated with four spots of argon green laser photocoagulation per eye. After 7 days of laser, the inflammatory and pro-angiogenic profile was analysed by qPCR assay while the protein levels of α2M and LRP1 were studied by WB. On choroid–RPE flatmounts stained with isolectin B4 (endotelial marker), the localization of mononuclear phagocyte cells and its levels of LRP1 were evaluated with F4/80 and Iba1 staining (macrophage and microglia) by IF by confocal microscopy. LRP1 levels on microglia were confirmed by Flow cytometry. We could observe on CNV animals high levels of both, pro-inflammatory and pro-angiogenic factors, as well as an elevated number of mononuclear phagocyte cells expressing LRP1 close to the CNV area. In this sense α2M and LRP1 showed change of expression, particularly on microglia cells. Further studies are needed to know the role of α2M/LRP1 on the CNV.

DISORDERS OF THE NERVOUS SYSTEM

The impact of metabolic syndrome on the progression of Parkinson's Disease: Preliminary results in the PPMI study database.

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Introduction. Metabolic syndrome (MetS) and Parkinson's disease (PD) share common pathophysiological mechanisms. This study aimed to investigate the contribution of MetS on the progression of Parkinson's Disease. Methods. We included 423 newly diagnosed PD patients, free from antiparkinsonian treatment, from the Parkinson's Progress Marker Initiative (PPMI) study database. We compared the changes in MDS-UPDRS total score (a marker of disease severity) and sub-scores in PD patients with or without MetS during the first five years of follow-up. Results. As shown in Table 1, PD patients with MetS were more frequency males. Patients with PD and MetS showed higher MDS-UPDRS total scores at baseline and during the whole follow-up as compared to those without (Figure 1, Table 2). Similarly, PD patients with MetS had higher MDS-UPDRS part III subscore (motor symptoms) at baseline and during the whole follow-up (Table 2). Conclusions. We observed that patients with MetS suffered from a more severe Parkinson's Disease, manifested by higher MDS-UPDRS total score at the clinical diagnosis of the disease and during the first five years of follow-up. These preliminary results suggest that MetS may contribute to the neurodegenerative process of Parkinson's Disease.

DISORDERS OF THE NERVOUS SYSTEM

Bone marrow mononuclear cells, an important player in peripheral nerve regeneration

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Bone marrow mononuclear cells (BMMC) is an heterogenous fraction containing a small population of multipotent cells. BMMC are good candidates for cell therapy because of their convenient isolation protocol, high yield and survival rate after transplantation and low immunogenicity.
We have demonstrated the spontaneous migration of endogenous CD34+ multipotent cells both in a reversible and irreversible model of Wallerian Degeneration. The aim of the present work is to evaluate systemic transplantation or endogenous mobilization of BMMC as a potential therapy for different sciatic nerve injuries. For this, adult rats were submitted to different experimental models of sciatic nerve damage and morphological, functional and pain behavior parameters were evaluated. In all these models BMMC migrated exclusively to the injured nerve and were able to prevent or revert the neuropathic pain associated to the injury. BMMC also demonstrated beneficial effects in terms of morphology, compound muscle action potential and sciatic functional index. These effects can be potentiated with combination of BMMC with magnetic nanoparticles.
Pharmacological stimulation of endogenous CD34+ cell migration through AMD3100 also demonstrated a recovery in myelin protein organization in terms of MBP and PMP22, 7 days post injury.
These results encourage us to propose BMMC systemic transplant or pharmacological mobilization as a promising strategy for the treatment of acquired peripheral neuropathies.

DISORDERS OF THE NERVOUS SYSTEM

Neurodegenerative diseases and neuronal plasticity: towards new therapeutic strategies in TDP-43 proteinopathies using murine preclinical models.

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Maintenance of proper protein homeostasis is an essential activity of mammalian cells. Alterations at the level of RNA binding proteins (RBPs) have recently been described as a central event in many pathologies and often play a central role in neurodegenerative (ND) diseases. One of the main RBPs involved in these processes is TDP-43, particularly in the ND pathologies Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). Our general objective is to study whether changes in neuronal activation and plasticity play a role in TDP-43-mediated pathogenesis using a murine model of proteinopathies. In particular, we will use transgenic mice that conditionally overexpress a mutated cytoplasmic form (TDP-43-ΔNLS) of human TDP-43 in forebrain neurons in order to: a) establish the impact of local/global changes in neuronal activation and plasticity in the behavioral deficits mediated by alterations in TDP-43; and b) determine if the pharmacological modulation of the BDNF/TrkB pathway (which regulates neuronal activity/plasticity) using the drug LM22A-4 has therapeutic potential in our preclinical ALS/FTD model. Using approaches at biochemical, pharmacological and behavioral levels, we aim to analyze the pathophysiological roles of TDP-43. The results of this project will allow us to shed light on the pathogenic mechanisms underlying TDP-43 proteinopathies, which in turn will be vital to development new and more effective therapies targeting this group of diseases.

DISORDERS OF THE NERVOUS SYSTEM

Role of purinergic signalling in counteracting excitotoxic damage induced by kainic acid in a model of spinal injury

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Spinal cord injury (SCI) is a devastating condition often accompanied by motor functional deficits and neuropathic pain. The pharmacological agents used for motor and sensory symptoms treatment after SCI are up to now inadequate. Our previous studies were focused on understanding different stages of the secondary process and SCI key mediators that allow early neuroprotection to be effective. Our objective is to evaluate the role of purinergic signalling to trigger SCI after chemical injury. We have now shown that 1h kainate (100 µM) application largely damages neurons via excitotoxicity (Mazzone et al, 2010). Release of endogenous glutamate and ATP during experimental protocols mimicking SCI in vitro could be reliably monitored on a real-time basis with a commercially available biosensor. Our data indicate a higher glutamate and ATP release induced by kainate. We have also analyzed the effect of Coomassie brilliant blue G (10 mM, BBG), a non-nucleotide purinergic antagonist, to find out the consequences on neurons and glial cells after pharmacological block. Immunohistochemistry indicated a much larger loss of neurons using kainate followed by BBG, without effect on astrocytes. Thus, our data indicate that early release of ATP after excitotoxic damage may affect neuronal survival, with a potential effect on network plasticity and implications for neuroprotective strategies. Supported by ICTP, SISSA, Universidad Austral and CONICET.

MY PHD THESIS PROJECT

Inter-hemispheric asymmetries in the population variances and covariances of measures characterizing the shapes and sizes of human brain regions

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So far, the description of neuroanatomical asymmetries of the human brain has focused on detecting brain structures in which the population mean of their size or shape differs significantly in the two cerebral hemispheres. Yet, in principle, asymmetries may exist also in higher moments of the distribution. In particular, asymmetries in the correlation structure of shapes and sizes of different brain regions provide relevant information in the diagnosis of anatomical anomalies. Negative correlations may reflect a competition of different brain areas to occupy the limited volume of the skull, so that an increase in one region must be compensated by a decrease in a neighboring one. Positive correlations probably reflect common evolutionary, epigenetic or ontogenetic factors dictating the final size or shape of a collection of developmentally or functionally connected regions. Here we propose probabilistic graphical models to describe these assymetries in a sample of 77 healthy volunteers aged 18-60 of both sexes, from Bariloche. Brain images were obtained with a 3T MRI scanner, and the obtained T1 images were segmented into 186 anatomical measures (thicknesses, areas and volumes) using the freely available software FreeSurfer. Our analysis confirms the results of previous studies reporting asymmetries in the population mean of the measures. In addition, it also describes several novel significant lateralization effects in their second-order correlation structure.

MY PHD THESIS PROJECT

Dynamics of cerebellar microglia during aging and aging-associated pathologies: impact of immunomodulators on the underlying neurodegenerative processes

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Previous studies have shown that the functional role of microglia in the cerebellum alters significantly as the brain ages. In this PhD thesis, we hypothesize that microglia are active participants in implementing cerebellar morphofunctional changes due to normal aging and may also contribute to the development of age-related pathologies. Furthermore, we hypothesize that some immunomodulators, such as melatonin, might effectively mitigate these deleterious microglia-mediated consequences. Our general approach is to study microglia participation under normal and pathological cerebellar physiological conditions. Microglia in young adults will be studied as a control, and these will be compared to microglia in healthy aged specimens, and to specimens under various neurodegenerative conditions. In addition, the immunomodulatory effects of melatonin on these processes will be examined. Cerebellar specimens for this study will be collected from 3- and 18-month-old male Wistar rats, and from genetically modified mice, such as APP/PS1; Cx3CR1-eGFP+/- mice (a model of Alzheimer's disease). For analysis, we are applying a multidisciplinary set of methods, including immunohistochemistry, confocal microscopy, and Western blot. Preliminary data generated from this study will be presented.

MY PHD THESIS PROJECT

Modulation of the Prefrontal Cortex-Amygdala circuit by early-life stress exposure and its impact on the stress response in prepubertal and adult rats.

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Chronic stress constitutes a major risk factor for the development of several affective disorders such as depression, anxiety and substance use disorder in adult individuals. The molecular mechanisms underlying the vulnerability to develop these diseases are thought to be related to alterations in the stress response, as well as dysregulations in brain areas that modulate its action and are fundamental in emotional processing. Among them, the role of the amygdala (Amy) and the prefrontal cortex (PFC) are crucial. The first stages of life are a fundamental period in the maturation of these structures, since genetic and environmental factors can reprogram their functioning and impact on the individual's subsequent response to stress. The aim of this project is to assess the impact of early-life stress on the stress response of female and male Wistar rats throughout the ontogeny. We will mainly focus on the PFC-Amy circuit since its dysregulation has been linked to the pathophysiology of affective disorders related to a malfunction of the stress system. We hypothesize that early-life stress will modify the structure and functioning of the PFC-Amy circuit leading to variations in the stress system of the offspring in a biphasic way: in the short term, these modifications could confer the exposed individuals an adaptive advantage in hostile environments; However, in the long term they might be deleterious, accentuating a predisposition to suffer from behavioral disorders.

MY PHD THESIS PROJECT

EXOCYTOTIC FUSION PORE MODULATION AND ITS EFFECTS ON ENDOCYTOSIS AND SECRETORY VESICLE REPLENISHMENT IN MOUSE CHROMAFFIN CELLS

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Vesicular fusion modes in neurons and neuroendocrine cells are associated to different recovery paths of new vesicles. While kiss-and-run implies fast membrane retrieval and “in situ” replenishment of intact vesicles, total collapse is followed by slower clathrin mediated endocytosis, and “de novo” generation, transport and maturation of vesicles. The first event that initiates fusion of vesicles to plasma membrane is the formation of a small fusion pore. Recent publications suggest that the fusion pore is finely regulated by a variety of proteins, which may modulate positively or negatively the opening of the pore, favoring the total collapse of the vesicle in the membrane or the closure of the pore (kiss-and-run). The main goal of this project is to study the relationship between fusion pore stability and the associated processes of endocytosis and secretory vesicles replenishment, after the exocytosis of the immediately releasable pool in mouse chromaffin cells. To reach this goal, we are going to express diverse proteins in primary chromaffin cell cultures, which alternatively promote pore stability (and closure) or pore opening. Variations in pore stability are going to be evaluated by amperometry, and endocytosis and IRP replenishment by cell capacitance measurements. We hypothesize that factors promoting pore closure will favor fast endocytosis and replenishment, while factors promoting pore opening are going to be associated to slow endocytosis and replenishment.

MY PHD THESIS PROJECT

Effects of early-life stress due to infant maltreatment on hippocampal physiology in juvenile rats

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Childhood maltreatment from the caregiver is associated with adverse brain development and increases the vulnerability to develop psychopathologies in later life. One of the brain structures most affected by infant maltreatment is the hippocampus (HPC). It contains high levels of stress hormone receptors, being an important modulator of the response mediated by the hypothalamic-pituitary-adrenal axis. In addition, since its maturation occurs during early childhood, the HPC is highly sensitive to stressful conditions such as infant maltreatment. The disturbance of the HPC causes cognitive and emotional disorders such as depression and post-traumatic stress. However, the current evidence on the effects of infant maltreatment focuses mainly on adults, whereas the effects at earlier ages are still poorly studied. Therefore, the aim of this project is to analyze, at the behavioral and molecular level, the impact of infant maltreatment on the hippocampal physiology of juvenile individuals using a model of infant maltreatment in rats. Our hypothesis holds that maltreatment during early childhood leads to modifications in the structure and function of the still developing HPC, resulting in behavioral and cognitive alterations that may be perceptible during the juvenile stages of the individual's life. Exploring the impact of child maltreatment on young individuals might help to the development of early interventions that seek to improve their health and quality of life.

MY PHD THESIS PROJECT

A nanotechnological neuroregenerative strategy using transfected multipotent cells.

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Peripheral neuropathies are high frequency events, comparable in prevalence to brain stroke and Alzheimer's disease. However, a suitable treatment to get full recovery is still difficult for health care providers and neuroscientists.
One limitation associated with nerve repair is the short window time available for therapeutic intervention. Thus, we focus on the development of new strategies to promote functional and morphological nerve regeneration and to prevent neuropathic pain development. Cell transplant combined with nanotechnological tools represent a novel and promising therapeutical strategy. Our group has demonstrated the effectiveness of the magnetic targeting of systemically transplanted adipose mesenchymal stem cells loaded with iron oxide nanoparticles as a neurogenerative approach. In addition, we demonstrated PEI-PLGA nanocapsules loaded with Sodium Fluorescein, and adsorbed/loaded with DNA as a successful non-viral transfection agent.
To take a step forward, the goal of the present project is to develop a magnetic poly lactic glycolic acid (PLGA) nanocapsule containing the mRNA/cDNA of trophic factors such as NGF, IGF-1, BDNF, GDNF or CNTF to transfect bone marrow mononuclear cells (BMMC) and stimulate cell migration and recruitment to the injured nerve with magnetic targeting. By this way, the combination of biological and nanotechnological tools may be used to shed light in nerve regeneration and to propose a potential acellular regenerative approach.

MY PHD THESIS PROJECT

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 (Bordone 2021). 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 generate 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.

MY PHD THESIS PROJECT

Exploring the AMPK signalling as a potential intermediate in yerba mate-induced neuroprotection

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The consumption of Yerba mate(YM), green tea and coffee are all negatively linked with the development of Parkinson's disease. They share several active compounds, remarkably polyphenols, such as chlorogenic acid(CGA). We showed that YM enhances survival of dopaminergic neurons in primary mesencephalic cultures. To investigate whether YM regulates intracellular mechanisms related with growth and survival of dopaminergic neurons, we focused on AMPK, a key signaling molecule involved in cell metabolism, strongly linked with neuroprotection and potentially activated by CGA.
As a first step to test this hypothesis, we have started with the simplified model of SHSY5Y neuroblastoma cell line. We have tested the phosphorylation status of AMPK at different concentrations and exposure times with an extract of YM and CGA. We have found that YM produced an increase in the phosphorylation of AMPK, and despite the mandatory stop produced by the pandemic, we have now produced additional preliminary results including treatment with CGA, as well the exploration of other regulatory molecules including an indirect marker of mTOR (pp70S6Kα),EGR-1 and ERK. The regulation of AMPK itself is a huge evidence of the involvement of this pathway, very attractive because of its role in paradigms of neuroprotection. Further and several work is still necessary to follow up this research line, but we have already settled down the bases of a new experimental line with a clear projection in the short term.

MY PHD THESIS PROJECT

6-OHDA-induce dopaminergic degeneration exacerbates anxiety-related behaviors in BDNF Val66Met mice

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A SNP in the BDNF gene is present in 25% of the world population with a distribution of 20% BDNFVal/Met and 5% BDNFMet/Met. The SNP results in a valine for methionine substitution at position 66 (Val66Met) within the BDNF prodomain (pBDNF) sequence.This SNP is highly associated with increase predisposition to develop anxiety, addiction and cognitive deficit in Parkinson's disease. All these disorders include CNS dopaminergic systems dysfunction, therefore, we hypothesize that the Met variant of pBDNF alters the structure and function of dopaminergic neurons and increase their vulnerability to degenerate. First, we found that the pBDNF and its receptors, p75NTR and SorCS2, are present in the ventral mecescefalon and striatum. Then, we studied in vivo if an external and specific dopaminergic neurotoxin 6-OHDA affects dopamine-related behaviors in the presence of at least one Met allele. Using anxiety-related and motor behavioral test, we determined that mice injected with 6-OHDA with at least one Met allele displays motor behavioral abnormalities like motor asymmetries in the OFT and CT. Additionally and very interesting, we observed that only BDNFMet/Met mice with 6-OHDA show increased anxiety-related behaviors in the OFT and in the LDT. All these results suggest that there is an additive effect between dopaminergic neurodegeneration in the Met allele carriers which could help explain the increased incidence of motor and mood disorders associated with the Val66Met SNP.

MY PHD THESIS PROJECT

Changes in the expression of endocannabinoid receptors and enzymes in primary afferent neurons from male and female animals with oxaliplatin-induced peripheral neuropathic pain.

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Oxaliplatin-induced peripheral neuropathic pain is a frequent and debilitating side effect of cancer therapy. The endocannabinoid system is one of the main neurotransmitter systems participating in pain control. Here we explored whether the development of oxaliplatin-induced allodynia correlated with changes in the expression of cannabinoid receptors (CB1 and CB2), non-cannonical receptors (GPR55, TRPV1 and 5HT1A), and the main enzymes involved in the synthesis (DAGLα, DAGLβ, NAPE-PLD) and degradation (MGL, FAAH) of endocannabinoids, in primary afferent neurons from both male and female rats. Animals receiving oxaliplatin developed mechanical and cold allodynia. No statistically significant differences were observed between sexes. Oxaliplatin induced significant changes in the expression of the different components of the endocannabinoid system in primary afferent neurons. The mRNA levels of CB1, CB2, TRPV1 and 5HT1A were found to be increased ($p<0,05$ vs CTL in all cases), while GPR55 was downregulated ($p<0,05$ vs CTL) in both male and female animals. While no changes were observed in DAGLβ levels ($p>0,05$ vs CTL in both cases), DAGLα was downregulated in male and upregulated in female rats ($p<0,05$ vs CTL in both cases). Finally, MGL and NAPE-PLD showed increased levels ($p<0,05$ vs CTL) only in male animals. Our results suggest that oxaliplatin-induced changes in the expression of cannabinoid receptors and enzymes in peripheral neurons could underlie pain development.

MY PHD THESIS PROJECT

PRELIMINARY STUDIES INVESTIGATING THE CENTRAL ACTIONS OF THC IN MICE

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Delta-9-tetrahydrocannabinol (THC) is the main psychoactive component of the Cannabis plant. The molecular mechanisms by which THC acts in the brain and their cross-talk with other endogenous neuroendocrine systems are just beginning to be investigated. Here, we evaluated the neuroanatomical and behavioral effects of the central treatment with THC in mice. First, we administered intracerebroventricularly (ICV) 5 mg of THC to wild-type male mice and assessed the induction of the marker of neuronal activation c-Fos 2-h after treatment as compared to vehicle-treated mice (n=4 and 3, respectively). We found that THC induced an increase of the number of C-Fos positive cells the supramammillary nucleus (SuM), whereas it did not change the number of C-Fos positive cells in other brain areas, such as ventral tegmental area (VTA), nucleus accumbens (Acb) and LHA. In parallel, we assessed acute and overnight food intake as well as on locomotor activity and conditioned place preference, and failed to find THC-induced effects. Thus, our preliminary data indicates that ICV administration of 5 mg of THC induces SuM activation without behavioral effects unmasked with the tested approaches. We have set up experimental conditions in mice to uncover central effects of THC, we hope to improve such experimental conditions to now investigate novel aspects of the THC action in the brain.

MY PHD THESIS PROJECT

Demyelination/Remyelination in the CNS: role of ODN IMT504 in the repair process

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Myelin is a highly specialized membrane which, in the CNS, is produced by oligodendrocytes (OLs). Demyelination is a pathological process characterized by myelin sheath loss from around axons, which results from genetic abnormalities, leukodystrophies, toxic demyelinating agents or inflammatory damage affecting both myelin and OLs. In turn, remyelination is the repairing response to demyelination and entails the restoration of myelin sheaths and the resolution of saltatory conduction and functional deficits. Multiple sclerosis is a high-incidence inflammatory demyelinating disease affecting young adults which involves demyelinated foci in different brain areas, sharp astrogliosis, microglial activation, persistent inflammation, and frequently unsuccessful remyelination. IMT504 is a non-CpG oligodeoxynucleotide consisting of 24 nucleotides (5`TCATCATTTTGTCATTTTGTCATT-3`) and characterized by 2 specific PyNTTTTGT sequences in its molecule, Py,being C or T and N being A, T, C or G. Based on IMT504 immunomodulatory effects and regenerative properties, this work aims to study the possible promyelinating effect of IMT504, either by acting on the polarization of microglia toward an M2 phenotype or by increasing the proliferation of OL precursors (OPCs) and their differentiation. To this end, IMT504 effects will be evaluated both in vitro, in primary cultures of neural stem cells (NSCs), OPCs and microglia, and in vivo, using the toxic cuprizone-induced demyelination model.

MY PHD THESIS PROJECT

Minocycline loaded chitosan nanoparticles for the prevention of relapse to cocaine seeking in a self-administration model

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Glia exerts a strong influence on cocaine-induced plasticity, releasing different mediators that alters excitatory transmission and neuronal signaling. Previous evidence of our lab demonstrated a central role of microglia in the disruption of glutamate (GLU) homeostasis in the nucleus accumbens (NAc) thought to underlie the stress-induced facilitation of cocaine self-administration. In this project we will evaluate microglia-dependent mechanisms associated to relapse of cocaine seeking behavior and neurobiological changes. For this purpose, we will use an animal model of cocaine self-administration administered with minocycline, (a potent inhibitor of microglia activation), in nanoparticles complexed with chitosan (NP-MINO) to facilitate their bioavailability to the brain. Specifically, we will evaluate the effect of NP-MINO on cocaine seeking behavior, and associated changes such us microglia activation, GLU homeostasis (GLT-1 receptor expression, GLU reuptake and spillover), structural modifications in dendritic spines and alterations in synaptic plasticity in the NAc. To carry out these objectives, we will use a combination of molecular, neurochemical and behavioral studies. This novel project will open new avenues towards the treatment of cocaine addiction. We expect that by restoring glial function with NP-MINO it will be possible to normalize the changes in GLU homeostasis and synaptic plasticity induced by cocaine and, thus, prevent drug-seeking behavior.

NEURAL CIRCUITS AND SYSTEMS NEUROSCIENCE

Maternal separation increases prefrontal synaptic innervations onto dorsal raphe neurons in the mouse developing brain

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Early adversity represents a main risk factor for the emergence of psychiatric disorders in adult life. In mice, postnatal days 2 to 14 constitute a critical period of vulnerability when stressors and environmental perturbations can alter the maturation of prefrontal circuits. Maternal separation (MS) has been well-established as a model to study the impact of early-life stress on neurodevelopment. MS during the critical period produces morpho-functional changes in the prefrontal cortex (PFC), accompanied by increases in depressive-like and anxiety behaviors. PFC descending circuits exert a top-down regulatory control over the dorsal raphe nucleus (DRN), the main source of forebrain serotonin (5-HT). Activation of PFC afferents in the DRN increases active stress-coping strategies and mood control. We studied whether MS during the critical period could modify the synaptic architecture of the developing PFC-to-DRN circuit. We analyzed the abundance of glutamatergic (vGLUT1/vGLUT2) and GABAergic (GAD2) synaptic afferents in the DRN after the last MS exposure (at day 15). Synaptic boutons were quantitatively analyzed using the high-resolution immunofluorescence technique Array Tomography. We find that MS increases the prefrontal innervations onto DRN neurons, without affecting either subcortical glutamate or GABA afferents. Our study indicates a selective developmental effect of stress on the PFC-to-DRN circuit, likely contributing to emotional vulnerability in the MS model.

NEURAL CIRCUITS AND SYSTEMS NEUROSCIENCE

Cortical rhythms are locked to auditory features of canary song

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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 cortical neurons of canaries (Serinus canaria), in response to auditory playback of the bird's own song. The rhythmic features of canary song allowed us to show that this large-scale synchronization was locked to defined features of the behavior. We recorded neural activity in a brain region where sensorimotor integration occurs, showing the presence of well-defined oscillations in the local field potentials, which are locked to song rhythm. We also show a correspondence between local field potentials, multi-unit activity and single neuron activity within the same cortical region. Overall, our results show that the rhythmic features of the vocal behavior are represented in a cortical region of canaries.

NEURAL CIRCUITS AND SYSTEMS NEUROSCIENCE

Processing of olfactory information in the brain of Drosophila melanogaster

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Odorants are detected by olfactory receptor neurons (ORNs) that project to the antennal lobe (AL), the first olfactory neuropil in the insect brain, where they make synaptic contacts with: i) projection neurons (PNs), that constitute the output of the AL; and ii) local neurons (LNs) that form a dense network of lateral interactions within the AL. The main goal of this project is to study the role of the LNs in odor representation using Drosophila melanogaster.
On a first approach we downregulated the expression of GABA-A receptors in PNs using RNAi and performed calcium imaging of odor-elicited activity in the AL. We found that constitutive reduction of the expression of the Rdl receptor subunit produced a series of compensations that resulted in the emergence of new inhibitory interactions. This result suggested the existence of a strong developmental plasticity in the AL.
As a second approach, we aim to acutely and reversibly block the activity of LNs. In that sense we plan to use shibire, a temperature sensitive mutant, to silence the LNs. Up to now, we tested the effect that raising the temperature of the flies has on odorant evoked activity at the AL. Preliminary results show that shifting temperature from 22 to 30°C, only faintly alters odor elicited calcium signals. This result opens the possibility to measure odorant representations with and without the contribution of the LNs in the same animal.

NEURAL CIRCUITS AND SYSTEMS NEUROSCIENCE

Learning induces signatures of context-dependent processing in olfactory cortex

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Primary sensory cortices are considered as brain regions functionally specialized to encode physico-chemical attributes of the sensory environment. However, the animal's internal state as well as its ongoing motor behavior can affect cortical activity. In the present work, we study how activity in the primary olfactory cortex of mice is modulated by sensory and non-sensory variables related to a context-dependent olfactory decision-making task. For this, we recorded piriform cortex (PC) activity in head-fixed mice trained in a GO/NO-GO task where they explore a virtual corridor to learn that a specific odor is associated with a reward only when presented in a particular visual context. We found that, throughout task learning mice develop adaptive anticipatory behaviors and change their decision-making behavioral strategies, first learning to discriminate odors, then reducing their bias for GO responses, and finally associating odors to visual contexts.
Using statistical models of neuronal activity, we reveal that after learning, but not before, visual context can be successfully decoded from PC spiking activity. Furthermore, task variables such as odor, inhalation rate, virtual spatial position, locomotion speed, licking and reward strongly shape neuronal activity, inducing a reorganization of PC representations after learning. This suggests that the PC may use information from other brain areas to adapt odor processing depending on experience and behavior.

NEURAL CIRCUITS AND SYSTEMS NEUROSCIENCE

Exploring the contribution of lateral entorhinal cortex to piriform cortex neuronal coding

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The piriform cortex (PC), the main region of the olfactory cortex, receives afferent sensory inputs from the olfactory bulb (OB) through the lateral olfactory tract (LOT), and extensive inputs from higher-order areas such as the lateral entorhinal cortex (LEC). To understand the contribution of LEC to the processing of odors we study its functional connectivity to excitatory and inhibitory neurons in the PC. We infected LEC with adeno-associated virus expressing channelrhodopsin under CamKIIa promoter to activate excitatory LEC afferents arriving to PC. We recorded then, in acute brain slices, postsynaptic currents and spiking in pyramidal L2/3 neurons and interneurons, in response to photostimulation. We found that excitatory long-range projections coming from LEC evoke different excitation to inhibition balance in each type of neuron. L2 neurons and PV interneurons (PV-IN) receive more excitation than inhibition along a 10Hz stimulation train. We then explored mechanisms of plasticity of olfactory inputs in association with LEC activation and, our preliminary results suggest that association among those inputs results in a potentiated response to LOT afferents. Last, to assess the role of LEC in the processing of odors in vivo, we are conducting experiments to pharmacologically inactivate this region during an odor-visual context associative task and evaluate the effect of LEC inhibition after learning this olfactory behavior.

NEURAL CIRCUITS AND SYSTEMS NEUROSCIENCE

Reward mediate modulation of the evoked response in the primary visual cortex

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The primary visual cortex (V1) neuronal activity encodes basic properties of visual stimuli. Experience dependent plasticity has been observed in V1 as a way to improve visual perception. However, recent studies show that V1 neural plasticity is also related to reinforcement learning. When rodents experience an association between a visual stimulus and a contingent future reward, a proportion of V1 neurons develop reward timing activity. Cholinergic projections from the basal forebrain (BF) have been shown to be necessary and sufficient to induce the reward timing activity in V1. However, little is known about whether this activity evolves simultaneously in the BF and V1 during learning. To unveil this, we will implant C57BL/6 adult male mice with electrodes in V1 and BF and record electrophysiological activity in head-fixed mice learning a visually cued rewarded task. So far, we trained three mice that successfully learned the task, showing an increase of correct trials from 47% to 99% and we identified a high percentage of V1 neurons that report reward timing after training. We found the three types of reward timing activity that have been reported: a sustained increase in response until the reward was expected, a sustained decrease in response until the reward was expected and a peak response at reward time. Rewarded and unrewarded trials evoked the same responses. To continue with the project, we plan to carry out simultaneous recordings on V1 and BF.

NEURAL CIRCUITS AND SYSTEMS NEUROSCIENCE

Place cells activity correlates with the memory expressed in an unrewarded contextual memory task

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Place cells (PC) are hippocampal neurons that are tuned to spatial location and are able to change their tuning when sensory inputs change (remapping). Collectively, they are thought to form the neural basis of a cognitive map and provide the spatial dimension of episodic memory. Moreover, it has been suggested that the hippocampal ability of storing and distinguishing between different situations and contexts can be related with PC's remapping.
Several studies have shown how PC can either remap or not as a consequence of changes in the environment. However, it is still unclear the role that PC have in episodic memory. The aim of this project is to understand how the PC activity of CA1 and CA3, two hippocampal regions, correlates with the evocation of contextual memories. To tackle this question we performed electrophysiological recordings in CA3 and CA1 while the animal was performing a task that allows us to discriminate if it recognizes a context as new, or as one it already knows. We found a significant correlation between CA3 PC activity and the memory that the animal is recalling. In particular the amount of remapping and the spatial correlation of PC activity between contexts is related with the animal's behavioral output. These results suggest that PC activity not only is important for spatial navigation but also for evocation of contextual memories.

NEURAL EXCITABILITY

Role of connexin 43 from olfactory ensheathing glia on olfactory nerve repair.

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Olfactory ensheathing cells (OECs) are specialized glia forming connexin 43 (Cx43)-mediated networks whose processes surround olfactory sensory neuron (OSN) axons within the olfactory nerve and throughout the olfactory bulb (OB) surface. OEC neurotrophic properties are well documented, however approaches using in vivo selective manipulations to address their role in neurogenesis and integration of OSNs remain scarce. Our hypothesis is that Cx43 is necessary for the full expression of OEC neurotrophic properties and modulates the incorporation of new OSNs to the olfactory circuit. Our goal is to determine the effect of reducing the expression of glial Cx43 on the incorporation of new OSNs to the olfactory circuit, in a model of olfactory nerve damage. To do this, we will evaluate the generation, maturation and integration of OSNs by immunohistochemistry using markers of proliferation, maturity and functional connectivity in mice genetically modified to reduce the expression of Cx43 in OECs. According to our hypothesis, we expect a decrease in cell proliferation, as well as a delay in the maturation of OSNs, in Cx43-deficient mice. Furthermore, we expect to observe indicators of deficient innervation of the OB associated with the lack of Cx43. The relevance of this study lies in its contribution to identify mechanisms underlying OEC neurotrophic properties, relevant for the development of therapies for traumatic or degenerative pathologies of the nervous system.

NEURAL EXCITABILITY

Ghrelin treatment leads to dendritic spine remodeling in hippocampal neurons and increases the expression of specific BDNF-mRNA speciesGhrelin treatment leads to dendritic spine remodeling in hippocampal neurons and increases the expression of specific BDNF-mRNA species.

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Ghrelin (Gr) is an orexigenic peptide that acts via its specific receptor, GHSR-1a distributed throughout the brain, being mainly enriched in pituitary, cortex and hippocampus (Hp) modulating a variety of brain functions. Behavioral, electrophysiological and biochemical evidence indicated that Gr modulates the excitability and the synaptic plasticity in Hp. The present experiments were designed in order to extend the knowledge about the Gr effect upon structural synaptic plasticity since morphological and quantitative changes in spine density after Gr administration were analyzed "in vitro" and "in vivo". The results show that Gr administered to hippocampal cultures or stereotactically injected in vivo to Thy-1 mice increases the density of dendritic spines (DS) being the mushroom type highly increased in secondary and tertiary extensions. Spines classified as thin type were increased particularly in primary extensions. Furthermore, we show that Gr enhances selectively the expression of BDNF-mRNA species.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Protective roles of imidazolium salts in C. elegans models of neurodegeneration

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In this study, we aim to evaluate the role of imidazolium salts as antioxidant and anti-aging agents. We synthesized imidazolium salts and use the nematode C. elegans to perform a screening and analyze their ability to improve oxidative stress resistance. We identified a derivate, 1-Mesithyl-3-(3-sulfonatopropyl)imidazolium (MSI), that enhances animal resistance to oxidative stress.
As a first approach to delineate its mechanism of action, we evaluated MSI ability to activate transcription factors involved in cytoprotective stress responses, such as the DAF-16/FOXO and SKN-1/Nrf2 pathways. We found that MSI stress protection was not dependent on DAF-16. Nevertheless, we discovered that GST-4 detoxifying enzyme, a downstream effector of SKN-1, is involved in MSI-mediated oxidative stress resistance.
Oxidative stress has been largely related to aging and neurodegeneration. To gain insight into MSI role in proteostasis, we evaluated mobility as an indicator of healthspan in Huntington's, Parkinson's and Alzheimer's disease models. We found that MSI ameliorates mobility rate decline in these proteotoxic models of neurodegenerative diseases. Surprisingly, our results show that MSI did not improve mean lifespan neith.er in wild-type worms nor in Alzheimer's disease animal models. Overall, our results show a scenario where healthspan seems to be uncoupled to lifespan. Additional research is needed to underpin the mechanism responsible for MSI's protective role.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

EFFECTS OF ORAL Lactobacillus spp. PRETREATMENT ON BEHAVIORAL RESPONSES TO REPEATED SMOKED COCAINE

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Emerging evidence assigns a role of intestinal microbiota (IM) and bidirectional gut-brain axis in mood disorders. However, studies addressing the involvement of IM in substance use disorder (SUD) are limited. It has been shown that cocaine administration induces gut dysbiosis and chronic treatment with antibiotics enhances its rewarding property. Accordingly, we have recently demonstrated that repeated exposure to volatilized cocaine alters the structure and diversity of the rat IM. In this sense, IM modulation by probiotic bacteria could attenuate cocaine behavioral changes. The present study aims to evaluate if chronic oral administration of three probiotic Lactobacillus strains (L. johnsonii; L. rhamnosus; L. reuteri) prevents the behavioral effects induced by the repeated exposition of a smokable form of cocaine in rats. Animals were pretreated via oral syringe-feeding with the bacterial mixture (1x10E8 CFU in 0.5 ml skim milk) or vehicle (skim milk) for 28 days. During days 22 to 28, rats were daily exposed to cocaine (25 mg) by pulmonary inhalation and the locomotor activity was assessed. Preliminary results indicate a progressive stimulant effect of cocaine (locomotor sensitization) while bacteria do not seem to prevent this effect. Ongoing experiments will confirm these results. Additionally, anxiety and depressive-like behaviors will be addressed. Our findings will contribute to understand the role of IM and the potential therapeutic of Lactobacillus strains in SUD.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Activation of cannabinoid CB1 receptors in the nucleus accumbens core decreased basal extracellular glutamate after extinction of cocaine-conditioned place preference

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Previous findings from our lab have demonstrated pharmacologically that the cannabinoid CB1 receptors (CB1Rs) within the nucleus accumbens core (NAcC) mediates restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference (CPP), through modulation of the context-specific glutamate release after stress. Given that restoration of impaired accumbal glutamate homeostasis in cocaine-experienced rats prevented reinstatement, we proposed that the underlying mechanism to explain our previous observations could be related to the role of CB1R in modulating the basal extracellular glutamate levels. For this purpose, we employed the reverse microdialysis technique to locally and continuously perfuse increasing doses of ACEA, a highly selective CB1R agonist, and to collect extracellular glutamate within the NAcC of freely moving rats. Results showed that ACEA caused a reduction in the basal levels of extracellular glutamate in a dose-dependent manner. These in vivo findings are consistent with the canonical mechanism of action described for CB1R in accumbal slices and suggest that an initial reduction in basal levels of extracellular glutamate might result in lower inhibition of mgluR2/3, favoring the subsequent presynaptic glutamate release triggered by restraint stress in our model.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Neuroprotective effect of Palmitoylethanolamide pretreatment on HT22 murine hippocampal cells subjected to hypoxia-reoxygenation.

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Perinatal asphyxia (PA) is an oxygen deprivation that occurs around birth and alters neurodevelopment. We have recently revealed in vivo treatment with Palmitoylethanolamide (PEA) could attenuate early cytoskeletal dysfunction in CA1 hippocampal neurons and its behavioral correlate after PA (Herrera et al., 2018, 2020). In order to delve into the neuroprotective role of PEA against PA, we studied in vitro effects of PEA pretreatment in a murine hippocampal cell line HT22 subjected to hypoxia-reoxygenation. After incubation, cells underwent hypoxia for 24 h and 18 h of reoxygenation, or normoxia-reoxygenation in the respective controls. Cell viability was assessed using the MTT test. In a subsequent experiment, cultures were incubated with vehicle (absolute ethanol) or increasing doses of PEA (0.001, 0.1, 1, 10, 25, 50, 100 µM), 24 h before hypoxia-reoxygenation. Three cells were used for each dose tested and experiments were performed in triplicate. Our results revealed PEA pretreatment (100 µM) could significantly increase cell viability after hypoxia-reoxygenation. No toxic effect was observed in any of the tested doses. In a third experiment, cultures were incubated with vehicle (absolute ethanol) or PEA at a single concentration (100 µM) under the same experimental conditions. The number of viable cells was quantified by the trypan blue method. Similar results were found, reinforcing the protective role of PEA against hippocampal hypoxic insults. *Equal contribution.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Microencapsulation of rotenone: a useful tool to generate a model of Parkinson disease

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Parkinson`s disease (PD) is the second most common neurodegenerative disease in older people. In recent years, there was an increasing interest to develop experimental models of PD by using rotenone (ROT). As it was assayed previously by our group, microspheres allow a slow delivery of the drug and thus a long treatment with a single dose administration. In this work, ROT microspheres were prepared by an oil–water emulsion solvent evaporation technique. Microspheres loaded with ROT were physiochemically characterized by thermal analysis, XRPD and FTIR spectroscopy. Our previous pharmacological studies in Wistar male adult rats showed altered motor activity evaluated by behavioral tests.

The DSC thermogram of ROT microspheres showed a glass transition temperature (Tg) at higher values than the copolymer PLGA, suggesting both greater thermal stability and amorphous nature. In this sense, XRPD analysis showed a characteristic halo of amorphous compounds in agreement with DSC results. Evidences of intermolecular interactions between PLGA and ROT were not observed by FTIR analysis. In agreement with the experimental observations in rats, these results suggest that microparticles loaded with ROT could be a suitable tool to generate an animal model of PD.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Social Isolation induced cocaine sensitization during adolescence: is the sex of the rat an important factor

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Cocaine use disorder is a chronic disease characterized by the loss of control over drug-seeking and taking. It has been shown that transition between social use and loss of control, is mainly observed in vulnerable users; such susceptibility depends on environmental and biological factors. Our group is focused on understanding the role of Social Isolation (SI), as an environmental factor, and sex as biological factor, in the vulnerability to cocaine exposure in rats. Recently, we showed that 5 days of SI from postnatal days 30 to 35 (PND30-35) increases the response to cocaine in adult male rats. Also, previous results showed different behavioral responses to isolation in male and female rats. In the present study, we evaluate if 5 days of SI (PDN30-35) would induce cocaine sensitization on PND45, in female and male rats. So far, our preliminary results show that cocaine (5mg/kg i.p.) induced a higher locomotor response in isolated female rats compared to non-isolated ones; while in males cocaine induced a similar response in both groups. However, more animals need to be run to draw a conclusion. Moreover, animal's behavior during habituation will be analyzed. While future experiments will evaluate the levels of b-catenin in Prefrontal Cortex as a measured of Wnt pathway activity. Our working hypothesis is that SI increases cocaine vulnerability by decreasing the activity of Wnt canonical pathway in PFC in a sex dependent manner.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

SIGMA-1 RECEPTOR AGONIST PRE-084 ALTERS, IN TERMINAL BUT NOT IN EARLY ADOLESCENT FEMALE WISTAR RATS, ETHANOL-INDUCED CONDITIONED TASTE AVERSION, BUT DOES NOT AFFECT ETHANOL BINGE DRINKING

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Previous research shows reduced sensitivity to the aversive effects of alcohol in adolescence relative to adults. Moreover, recent work has suggested that aversive effects of ethanol are greater in late adolescence than in early adolescence but few studies have assessed the role of the different transmitter systems in these ontogenetic differences and even less in females. It is known that Sigma-1 Receptors (S1R) are involved in several manifestations of alcohol addictions such as ethanol drinking and conditioned taste aversion (CTA) which can be considered as a behavioral index of ethanol´s motivational properties. We found that pretreatment with the selective S1R agonist PRE-084 (32 mg/kg) altered ethanol(1,75 g/kg)-induced conditioned taste aversion (CTA) at late adolescence in female wistar rats but failed to affect ethanol(2,25 g/kg)-induced CTA at early adolescence. The effect of S1R agonism by PRE-084 (32 mg/kg) on binge ethanol intake was assessed at terminal adolescence. S1-R activation at the acquisition of ethanol induced CTA facilitated the extinction of such learning at terminal but not at early adolescence. PRE-084 did not significantly affect ethanol binge drinking in the terminal adolescents. The current report highlights the role of S1-R in ethanol-induced CTA and suggests that differential functionality of this transmitter system may underlie age-specific sensitivities to the aversive effects of ethanol.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Cross sensitization between stress and cocaine is associated to nuclear factor kappa B (NF-kB) activation in the nucleus accumbens

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Stressful experience-induced cocaine-related behaviors were associated with a significant impairment of glutamatergic mechanisms in the nucleus accumbens core (NAcc). NF-kB, a ubiquitous transcription factor, induce the expression of gene targets tightly linked to glia maintenance of glutamate homeostasis. Here, using a genetic and pharmacological strategy, we evaluate the impact of NF-kB abrogation in NAcc on the long-term expression of restraint stress-induced behavioral cross-sensitization to cocaine. Thus, we used lentiviral vectors expressing a dominant negative to the IKK (dn IKK) and the potent pharmacological inhibitor of NF-kB nuclear translocation, PDTC, to nullify the transcription factor activity. Chronically pre-stressed were administered intra-NAcc with dnIKK 7 days, or PDTC 20 minutes before a cocaine challenge administration, respectively. After treatment, behavioral sensitization and NF-kB levels were evaluated. Repeated stress induced a significant NF-kB activation in the NAcc. Consistently, the pharmacological or genetic inhibition of NF-kB activation, was sufficient to prevent stress-induced sensitization to cocaine. These results suggest a central role of NF-kB on the long-term neurobiological mechanism induced by stress in the NAcc, promoting the expression of cross-sensitization to cocaine. Furthermore, our findings help to understand the neural and molecular basis of the comorbidity between exposure to stress and cocaine abuse.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Development of a mouse model of haloperidol-induced vacuous chewing movements

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The development of tardive dyskinesias (TD) is frequently associated with chronic antipsychotic treatment in schizophrenic patients. These movement disorders have a high prevalence, reaching approximately 60%. TD can persist even after many years of discontinuation of the drug that triggered them, and become an irreversible phenomenon. There is no effective treatment that allows an acceptable solution to the problem, so it is important to advance in an adequate knowledge of the alterations that underlie its appearance to minimize the deterioration in the quality of life of patients. To study whether the development of TD induced by chronic treatment with haloperidol correlates with a modification of striatal synaptic connectivity, we have developed a model of vacuous chewing movements (VCM) in mice. Wild-type mice received a daily dose of 1.5 mg/kg of haloperidol for 30 days, then the dose was increased to 2 mg/kg for a further 30 days and behavior was observed every 5 days. After 60 days, the treatment was discontinued and the behavior was observed for a further 30 days. Orofacial movements were recorded: protrusion of the tongue, wide-range chewing movements, subtle chewing movements, and jaw tremors. Anxiety-like behavior was also assessed with the open field test and the light-dark test. With this haloperidol administration protocol we were able to induce the development of VCM of great intensity that lasted even after the pharmacological treatment was discontinued.

NEUROCHEMISTRY AND NEUROPHARMACOLOGY

Unravelling the physiological role and molecular function of betaine-sensitive nicotinic receptors of Caenorhabditis elegans

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The free-living nematode Caenorhabditis elegans is a model of parasitic nematodes. It has one of the most extensive nicotinic receptor (nAChR) families. However, the molecular functional properties and roles of many of these nAChRs remained unknown. ACR-23 is a nAChR present in neuronal and muscle cells of nematodes and it is not conserved in vertebrates. It is a cation-selective channel activated by betaine (BE) and sensitive to monepantel (MNP), a novel anthelmintic drug. Given the limited information about its functional role in nematodes, we explored ACR-23 from a physiological and molecular perspective. Locomotion assays of adult worm showed that BE significantly increased their motility. This effect was not observed in acr-23 mutants, indicating that BE acts through ACR-23. Interestingly, BE did not affect L1, indicating differential sensitivity between stages, probably arising from changes in ACR-23 expression levels during development. MNP decreased worm motility in the adult stage in a concentration-dependent manner with an EC50 of ~30 µM. The acr-23 mutant showed different MNP sensitivity compared to the wild-type strain, indicating that besides ACR-23 other receptors may be targeted by MNP. By using a primary culture of C. elegans muscle cells, we described for the first time the properties of BE-elicited single-channel currents. Our study provides insights into the molecular basis of anthelmintic action, which pave the way for the development of novel drugs.

NEUROENDOCRINOLOGY AND NEUROIMMUNOLOGY

Functional aspects of growth hormone secretagogue receptor expression in the lateral hypothalamic area of male mice

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Ghrelin is a stomach-derived hormone that promotes a variety of functions and acts via the growth hormone secretagogue receptor (GHSR). GHSR is highly expressed in the brain including the lateral hypothalamic area (LHA), a region involved in feeding behaviors, locomotor activity and reward-related behaviors, among others. Here we used male C57BL6 mice to gain insights into the functional aspects of the GHSR-expressing neurons of the LHA (GHSR-LHA neurons). First, we found that intra-LHA infusion of ghrelin increased food intake and transiently increased locomotor activity. Also, intra-LHA infusions of ghrelin increased the levels of the marker of neuronal activity c-Fos in the arcuate nucleus (involved in food intake regulation) but not in the LHA. Finally, we used an adeno-associated virus expressing Cre recombinase to restore GHSR expression in GHSR-LHA neurons of GHSR-deficient mice. Preliminary data indicate that re-expression of GHSR exclusively in the LHA may increase some reward-related behaviors such as consumption of high-fat diet in a binge eating model. Thus, GHSR expression in the LHA may mediate food consumption, locomotor activity and reward-related behaviors.

NEUROENDOCRINOLOGY AND NEUROIMMUNOLOGY

Correlation between cognitive impairment and biochemical parameters in Impaired Fasting Glucose (IFG) patients

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Type 2 Diabetes (DBT2) is a metabolic syndrome characterized by an increase in glucose and insulin blood levels. This syndrome is closely related to neurodegeneration and central nervous system damage.
Impaired Fasting Glucose (IFG) is the first step in DBT2 development, with fasting glucose levels between normal and DBT levels. Our previous results showed that patients with IFG exhibited significantly less score in a battery of cognitive tests called the “SAGE test” that evaluate different cognitive skills such as time-space orientation, short term memory, attention, construction of simple forms and associative memories. As cognitive decline in IFG has not been described yet, we investigated the relation between the overall SAGE test scores and different parameters. No correlation was found between the overall SAGE score and the age of the participants, or between the score and total cholesterol levels.
As inflammation is a risk factor for different degenerative diseases, we evaluated the plasmatic levels of IL-1β and TNFα. No significant difference was found between control and IFG patients. Additionally, there was no correlation between SAGE score and either of these proinflammatory cytokines. However, when we analyzed the dataset using multiple linear regressions, we found a significant association between SAGE scores, glucose and IL-1β levels which would suggest that inflammation would be one of the factors involved in cognitive impairment associated to IFG syndrome.

NEUROENDOCRINOLOGY AND NEUROIMMUNOLOGY

IGF1 gene therapy modifies hypothalamic microglia and delays reproductive senescence

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The process of aging affects the whole body including the central nervous system, where the hypothalamus plays a key role in the regulation of aging mechanisms. It has been described that a hypothalamic proinflammatory environment leads to reduce gonadotropin-releasing hormone (GnRH) secretion and affects Kisspeptin neurons.
We postulate that reducing proinflammatory processes with neurotrophic factors, may preserve Kisspeptin system and decelerate the aging process. For this, we implemented intrahypothalamic Insulin like Growth Factor 1 (IGF1) gene therapy providing to middle-aged female rats. We evaluated therapy effects on microglial cells response, and Kisspeptin and GnRH neurons. Rats treated with IGF1 gene therapy showed higher Kisspeptin expression in the anteroventral periventricular nucleus (AVPV) and a greater immunoreactivity of GnRH in the arcuate nucleus (ARC) and medium eminence. Moreover, IGF1 treated animals displayed an increased number of Iba1 cells and double immunoreactive (MHCII/Iba1) microglial positive cells in both the AVPV and ARC. In conclusion, IGF1 gene therapy maintains Kisspeptin production in AVPV and induces GnRH release in the median eminence and modifies microglia cells number and reactivity in middle-aged female rats. Our findings lead to postulate that IGF1 gene therapy, implemented before the first signs of reproductive cessation, has a protective effect against the reproductive decline.

SENSORY AND MOTOR SYSTEMS

The medial olivocochlear system alters the development of the auditory pathway.

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The auditory system of many mammals develops after birth. Before the onset of hearing, inner hair cells (IHC) are innervated by auditory nerve fibers and transiently by neurons of the medial olivocochlear (MOC) system. During this period, IHCs exhibit periodic depolarization patterns inducing stereotyped bursts of action potentials that are transmitted to the auditory circuits in the brain and promote neuronal survival, physiological maturation, and the proper establishment of the tonotopic map. It has been proposed that the MOC system may be a modulator of this activity. In addition, it has an important role in the protection from noise-induced hearing loss in adult rodents. Here, we evaluated the function of this transient synapse and the consequences of an early acoustic exposure during this critical period by using mice with genetic enhancement or ablation of MOC activity. We found that mice with enhanced MOC function have an earlier onset of hearing compared to mice with normal MOC synapses. In contrast, a delay was observed in mice with no MOC activity, suggesting that cochlear maturation is slowed in the absence of pre-hearing efferent modulation. Moreover, we observed that the maturation of the auditory system begins in the periphery and continues after the onset of hearing. Exposure to loud noise at this early stage, produced an alteration in the auditory sensitivity in mice with normal MOC while no changes were observed in those with enhanced function.

SENSORY AND MOTOR SYSTEMS

GABA and ACh are co-released from olivocochlear efferent terminals

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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 α9α10 nicotinic receptors 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 GABAB receptors in MOC fibers in the inner spiral bundle. Moreover, the application of GABAB agonists reduces ACh release. Transgenic mice expressing channelrodhopsin (ChR2) under the control of either GAD (GABAergic) or ChAT (cholinergic) promoters were used in this study. Here we show for the first time, that optogenetically activated fibers in GAD-cre/ChR2 mice (n=7) produced postsynaptic responses that were blocked with cholinergic antagonists (n=3). In addition, pharmacological experiments in ChAT-cre/ChR2 mice indicate GABAB activation, suggesting GABA release by cholinergic neurons (n=4). ChAT-cre/TdTomato cochleas, co-stained with antibody against GAD, showed a co-localization of GABAergic and cholinergic terminals in the inner spiral bundle. Altogether these results strongly suggest that ACh is being co-released with GABA from MOC fibers.

SENSORY AND MOTOR SYSTEMS

Gradient expression of ASIC1 channels in the spinal cord in the formalin acute pain mouse model

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Formalin test is used to assess acute pain responses in rodents to a formalin injection of the hind paw. Pain models were initially established in rats and then applied in mice. However, nerve anatomy differs between the species and within strains (Rigaud et al., 2008). This could have important consequences on how tissue areas should be processed after performing these tests.
Acid-sensing ion channels (ASICs) play important roles in pain conditions. ASIC1a contributes to spinal processing of inflammation-related pain behaviors (Duan et al., 2007), and peripheral inflammation increases the expression of ASIC1a in the rat spinal cord (Wu et al., 2004). On the other hands, Psalmotoxin-1 (Pctx-1), a toxin that inhibits ASIC1a, and an ASIC1a antisense oligodeoxynucleotide, have been shown to affect the response to formalin test (Mazzuca et al., 2007). Little is known about ASIC1 protein levels in some models, as protein levels proved difficult to detect.
We decided to analyze ASIC1a protein levels in the mouse acute formalin model at different lumbar segments in the spinal cord of C57BL/6 mice. Our results showed that the biphasic behavior of mice to formalin was accompanied by an increase in ASIC1 levels following a gradient stronger at L3 levels and decreasing towards L5 in formalin-injected mice. This work highlights the role of the ASIC1 channel in pain, focusing by areas to avoid a dilution effect and the potential role of pharmacological therapies aiming to this channel.

SENSORY AND MOTOR SYSTEMS

Birds breathe at an aerodynamic resonance

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Sustaining the high aerobic metabolism of endotherms requires continuous, life-long motor activity to ventilate the respiratory organ. In the unique respiratory system of birds, both respiratory phases are active. Inspiratory muscles expand the thoracic cavity, and, unlike in mammals, the lack of a diaphragm mandates active compression of the air sac system for expiration. Airflow can be regulated by multiple valves (glottis, syrinx and two sets of aerodynamic valves) arranged in series along the respiratory pathway. Given the complex morphology of the airways and the high energetic demand of sustained breathing, it is an important question to what degree this system is efficiently operated. To address this question, we investigated quiet breathing in canaries (Serinus canaria). We present a dynamical model for the avian respiratory system and report the measurement of its variables in normally breathing birds. Fitting the parameters of the model, we are able to show that birds breathe at an aerodynamic resonance of their respiratory system. Furthermore, this model indicates the parameters that may facilitate a shift in the resonances, thus generating the possibility for other respiratory behaviors, such as panting and singing, to be executed optimally.

SENSORY AND MOTOR SYSTEMS

Expression of ASIC1 channels in the Anterior Cingulate Cortex in the formalin induced acute pain mouse model

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The hindpaw formalin injection test (an acute pain behavior test) may be useful to highlight pain mechanisms relevant to patients in the clinic. In mice it elicits a biphasic response: the first, linked to stimulation of the primary sensory neuron; the later, associated with inflammation and central sensitization.
This model is used to analyze, in each phase, the role of specific channels as well as the effect of drugs targeting these channels. Acid-sensing ion channels (ASICs) regulate synaptic activity and play an important role in neurodegenerative and pain conditions. Prior injection of an ASIC1a inhibitor and antisense ASIC1a RNA has been shown to affect both phases of the test (Mazzuca et al. 2007).
Pain perception is thought to occur in the anterior cingulate cortex (ACC); human studies have reported that painful stimuli evokes activation of the ACC: the degree of which is correlated with the intensity of pain (Zhao et al 2018). Neurons in the ACC are activated in both acute and chronic pain states.
We analyzed ACC ASIC1 protein levels in a murine acute pain model using the formalin injection test.
Our results show a biphasic response to formalin. Pain behavior was accompanied by increased ACC ASIC1 levels contralateral to the injection site compared to ipsilateral, and greater than in controls.
This work highlights the influence of formalin induced pain on the expression of ASIC1 channels, which may constitute a potential therapeutic target of new pain therapies.

SENSORY AND MOTOR SYSTEMS

Song system neurons encode specific frequency range components in bird's own song

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The zebra finch (Taeniopygia guttata) is an oscine bird established as a model for studying the neural mechanisms involved in vocal production. As every oscine it has a telencephalic nucleus called HVC involved in the song learning, production and maintenance. One major characteristic is it's selective auditory responses to the bird's own song (BOS) in anesthetized or sleeping birds.
Zebra finches' songs have harmonics that can reach 20 kHz. A previous study showed BOS and low frequency enhanced BOS (increased relative power of frequencies below 1 kHz) evoke similar spike-count responses in HVC. However, an analysis of spike patterns demonstrated temporal coding information that discriminated between both stimuli, suggesting low frequencies are relevant for this nucleus.
There are no studies that evaluate which frequencies of BOS are necessary to elicit the auditory response in HVC. We recorded extracellular neural activity while the bird was asleep and used the BOS and filtered versions of it (f-BOS) as stimuli. We found HVC selective auditory response depends on the frequency range of the stimuli. Frequencies below 1.5 kHz are not enough for eliciting the same spike count as the original BOS. Contrarily, we found no differences in the spike-count elicited by BOS and f-BOS with frequencies above 5.5 kHz filtered (suppressed). These results suggest that frequencies below 5.5 kHz are relevant in auditory feedback and may be important for speech development and maintenance.

SENSORY AND MOTOR SYSTEMS

STUDY OF AUDITORY NEURONAL ACTIVITY IN A CORTICAL SENSORIMOTOR NUCLEUS IN CANARIES (Serinus canaria)

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The song of oscine birds is a behavior in which acquisition and production is mediated by a specialized set of neuronal nuclei called the "song system". Within the song system, the telencephalic nucleus HVC (proper name) is involved in the perception and production of song. Previous electrophysiological studies have shown that subsets of its neurons display selectivity, responding more intensely to the presentation of the bird's own song (BOS) than to almost all other sounds, as well as a precise auditory–vocal correspondence. The characterization of auditory responses in HVC has been developed mainly in sleeping or anesthetized birds. However, there are different reports regarding the neuronal response in HVC in awake individuals, depending on the species.
We analyzed recordings of extracellular neuronal activity in the nucleus HVC during the presentation of auditory stimuli in freely behaving male canaries (Serinus canaria). The bird's own song (BOS) was the target stimulus to study the neural response, while the song of a conspecific (CON) and the temporally reversed bird's song (REV) were used as control stimuli to assess the selectivity of the auditory response. The different types of neuronal responses obtained were categorized and their salient properties were quantified. For a particular case, the auditory neuronal response was compared with previous reports of premotor activity during song production to study the auditory–vocal correspondence in this species.

SENSORY AND MOTOR SYSTEMS

Neurotrophic factors regulate TREK2 expression in nociceptive DRG neurons

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TREK2 is a member of the 2-pore domain family of K+ channels (K2P) preferentially expressed by unmyelinated, slow-conducting and non-peptidergic isolectin B4-binding (IB4+) primary sensory neurons of the dorsal root ganglia (DRG). TREK2 controls the resting membrane potential (Em) of these neurons affecting their excitability. We showed that there is a re-distribution of TREK2 away from the cell membrane, resulting in a more depolarised Em, 7 days after spinal nerve axotomy (SNA) of the L5 DRG. IB4+ neurons depend on the glial-derived neurotrophic factor (GDNF) family of ligands to maintain their phenotype. In the SNA model, neurons are deprived of peripherally-derived trophic factors. Thus we hypothesized that they might control the expression of TREK2. Using a combination of immunohistochemistry, immunocytochemistry and western blotting we tested whether the members of the GDNF-family (GDNF, neurturin and artemin) and their receptors (GFRα1, α2 and α3) were involved in controlling the expression of TREK2 in the DRG. We found that TREK2 correlated strongly with the 3 receptors normally and that this correlation changed ipsilaterally for GFRα1 and GFRα2 and contralaterally for GFRα3 in the SNA model. Moreover, only GDNF restored IB4-binding and a normal expression pattern of TREK2 in cultured DRG neurons. This is the first demonstration that GDNF controls the expression of a K2P channel in nociceptors, a finding with therapeutic potential in the treatment of chronic pain.

SENSORY AND MOTOR SYSTEMS

Involvement of the mecensephalic locomotor region in motor learning

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Mammals have the ability to generate an infinite variety of motor behaviors, from simple actions such as walking to highly complex movements like object manipulation or speech. Some motor patterns are present at birth while new motor skills can be acquired through training and experience. Communication among numerous brain areas is needed to ensure accurate acquisition and execution of motor programs. However, the classical model for motor learning proposes that only a subset of structures along the motor command pathway within forebrain and cerebellum are subjected to activity-dependent adjustments and become reorganized during acquisition of a new skill. In contrast, downstream motor regions located in the brainstem are considered to be simple executive centers for stereotyped motor behaviors. In this study, we challenged this model by testing the role of the mesencephalic locomotor region (MLR) in learning the accelerating rotarod task. In this task, mice learn new motor strategies to stay in a rod that is rotating at increasing speed. Here we show that inhibiting protein synthesis in the MLR shortly after training during the early phase of motor learning affects the improvement in motor performance whereas the same treatment in expert animals has no effect. In conclusion, our preliminary data supports the role of MLR in the consolidation process of a new motor skill.

SENSORY AND MOTOR SYSTEMS

A consolidated view of neural activity in a cortical avian nucleus supports an integrated model for birdsong production

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Singing constitutes a complex learned behavior in songbirds. During song, the respiratory system and the vocal organ are driven by neural instructions from a set of nuclei dedicated to song production. This system is well-established as neuroethological model for understanding a range of fundamental biological questions pertaining to behavioral production, perception and learning, as well as relations of evolutionary and translational relevance.Telencephalic nucleus HVC (used as a proper name) plays a key role in the production of motor commands that drive the periphery. However, the precise nature of its involvement is yet to be resolved. 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, and we have previously shown good accordance of local field potential and single-unit activity with these predictions. In this work, we analysed multiunit activity from extracellular electrophysiological recordings in singing canaries (Serinus canaria). We compared this activity to the local field potential and to single-unit activity. We present a consolidated view in the singing animal in which all modalities agree with the proposed model and present activity locked to relevant features of the syllable being produced.

SENSORY AND MOTOR SYSTEMS

Role of cerebellum in nociception processing

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Classically described as a motor structure, the cerebellum is also implicated in a range of sensory behaviors such as nociception, emotion, learning, etc. Based on its anatomical and functional connectivity, we investigated the role of the cerebellar outputs in nociception modulation. We combined the use of a chemogenetic technique (DREADDs) expressed via viral vectors, finely tuning the activity of targeted structures, with acute nociceptive tests designed to assess the potential nociceptive modulation. Our results suggest that cerebellar outputs are implicated in nociceptive modulation and that this effect is carried out through specific glutamatergic cerebellar outputs pathways. In order to target glutamatergic cerebellar-thalamic pathways we combined the use of a CRE-recombinase expressing canine adenovirus-2 (CAV-2) with AAV-hSyn-DIO-hM4D(Gi)-mCherry (Inhibition) or AAV-hSyn-DIO-hM3D(Gq)-mCherry (Activation). We observed that thermal nociceptive responses evoked by the tail immersion, acetone and thermal place preference tests seems to be modulated by dentate(DN)-posteriomedial thalamus(Pom) and DN-centrolateral thalamus(CL) and DN-vetromedial thalamus(VM) projections. However, mechanical (Von Frey test) and chemical (capsaicin) nociceptive responses are controlled by DN-CL and DN-VM projections. In summary, our results suggest that distinct cerebellar-thalamic pathways are capable to modulate different modalities of acute nociception in rodents.

THEORETICAL AND COMPUTATIONAL NEUROSCIENCE

Encoding and decoding stimuli with mature and immature neurons of the dentate gyrus

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Heterogeneity plays an important role in diversifying neural responses to support brain function. Adult neurogenesis provides the dentate gyrus with a heterogeneous population of granule cells (GCs) that are born and develop their properties at different times. Immature GCs have distinct intrinsic and synaptic properties than mature ones and are needed for correct encoding and discrimination in spatial tasks. How immature GCs enhance the encoding of information to support these functions is not well understood. Here, we record the responses to fluctuating current injections of GCs of different ages to study how they encode stimuli. Immature GCs produce unreliable responses, exhibiting imprecise spike timings across repeated stimulation. We capture the encoding properties of the GCs by using statistical models to fit the stimulus-response transformation they perform. The obtained model parameters reflect the maturational differences of the population and indicate that immature GCs perform a differential encoding of stimuli. We then perform stimulus decoding using populations that contain GCs of different ages to study how age heterogeneity impacts the encoding of a single stimulus. We find that immature GCs enhance the fidelity of the signal transmitted by the population and improve the discrimination of similar time dependent stimuli.

THEORETICAL AND COMPUTATIONAL NEUROSCIENCE

Epistemology of neuroscience: Contributions from Canguilhem's perspective to the case of autism

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Based on "The normal and the pathological" (1943), an essay of the physician and philosopher Georges Canguilhem, epistemic aspects underlying the theoretical framework of neurosciences are discussed. For this author health is irreducible, dynamic and relational, showing that healthy and pathological states cannot be only quantitatively determined at a biological or statistical level. On the contrary, the pathological is mostly qualitative because it emerges from the individual experience of suffering and limitations, generated by a reduced capacity to change and to adapt to circumstances in a flexible and creative way. In addition, Canguilhem proves that biological, psychological or behavioral anomalies are not always pathological but depend on the assessment and value they receive from the individual as a whole at a given time and context. Autism has already been postulated as a paradigmatic disease model from Canguilhem's perspective, so we consider such contributions of canguilhemian epistemology should be considered and could be incorporated in the field of neurosciences.

TOOLS DEVELOPMENT AND OPEN SOURCE NEUROSCIENCE

Evaluating memory in large number of people using a gamified RULIT in an on-line platform

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Learning and memory processes are main research topics in neuroscience. Since they allow the execution of multiple manipulations on large numbers of subjects under strict control conditions, many fundamental studies are performed using animal models. Others are conducted in humans. They can still be done in controlled environments, but at the expense of costs and logistics that impact on the number of participants. Also, traveling to a laboratory introduces drastic changes to the participants' routine. Thus, intending to study memory processes on large numbers of people, with minimal impact on their routines, we developed a gamified version of the Ruff-Light task (RULIT) that runs on a web platform.

Here, we introduce this visuospatial task and show that people contacted through social media learned a secret path hidden within a labyrinth composed of multiple nodes. The participants accessed to a web page and followed a set of short instructions to perform the task. Then, independent groups were contacted by email to perform the memory retention test at 1, 3-4, 15, and 60 days. Memory expression was equivalent 1 and 4 days after training and remained for up to 2 months, but decaying in the function of time. Men showed better performance in training and test sessions than women.

In summary, we present a new tool for studying learning and memory processes remotely using the InvestigAr web platform.

TOOLS DEVELOPMENT AND OPEN SOURCE NEUROSCIENCE

Sentiment analysis in news media headlines in 2019 Presidential Elections: Exploratory Reliability Study Analysis

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Social networks offer the facility to access political news instantly. In recent years, given the spread of fake news, the role of news transmission in the political perception of citizens has been elucidated. Based on this, new computational models have been developed that seek to identify and predict subjective perception towards social content. Reliability has been a widely used tool in measuring agreements that different people arrive at the presentation of the same stimulus. Therefore, sentiment analysis could be a useful tool for analyzing electoral behavior. The purpose of this study was to evaluate the subjective perception of individuals for each presidential formula/force of principal Argentina´s newspapers during 2019 elections using reliability coefficient agreement. For this, 3 participants were recruited to classify 2257 headlines of the principal country's newspapers as positive, neutral, or negative according to their perception. To minimize ideological bias, each formula/force was
replaced by a "Target". Krippendorf nominal reliability alpha metric yielded adequate inter agreements between the participants. With this tool, we found that Fernandez was mentioned with a positive connotation in 1136 headlines(negative: 721), while Macri in 932
ones (negative: 1271). Other candidates did not exceed 420 positive mentions(negative<21). According to this, using these metrics could be a useful tool for future studies for classifying the valence of the headlines.