XXVII Congreso Anual de la Sociedad Argentina de Investigación en Neurociencias.

1-5 Octubre, 2012. Huerta Grande, Córdoba, ARGENTINA

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XXVII Congreso Anual de la Sociedad Argentina de Investigación en Neurociencias
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SAN Course:"Sculpting the Architecture and Physiology of the Brain: Hormones have a lot to Say!". Endocrine implications for developmental programming, reproduction and behavior

COURSE PROGRAM

Day 1 – Monday, October 1st
Developmental Programming

08:00-09:00 Registration

09:00-10:30 Lecture I: *Principles of Neuroendocrinology.* **Tony M. Plant**, Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine and Magee Womens Research Institute, Pittsburgh, USA.
This first lecture is intended to provide students knowledge of the basic concepts underlying the field of neuroendocrinology and therefore serve as a platform for more detailed consideration to further develop specific topics throughout the course.

10:30-11:00 Coffee break

11:00-12:30 Lecture II: *Impact of steroids during development: Sexual differentiation of the brain*. **María Julia Cambiasso**, Instituto de Investigación Médica Mercedes y Martín Ferreyra, INIMEC-CONICET-Universidad Nacional de Córdoba. Córdoba, Argentina
The main aim of this lecture is to examine the organizing effects of gonadal steroids on the Central Nervous System. Focus will be on the establishment of sex differences on neuron physiology and growth.

12:30-14:00 Lunch

14:00–15:30 Lecture III: *Neuroendocrinology around the World.* **Janete A. Anselmo-Franci**, Faculdade de Odontologia, Universidade de Sao Paulo; Riberao Preto, Brasil.
Neuroendocrinology is one of the main topics in neuroscience research; the INF is in charge of the diffusion of the activities related to it all around the world. It will be interesting to know how these activities are carried on and how students are able to participate in them.

15:30–17:00 Lecture IV: *When a baby is born, a mother is born: Role of postpartum hormonal status on maternal aggression and sexual behavior.* **Daniella S. Agrati Giadans**, Facultad de Ciencias; Universidad de la República (UDeLaR), Montevideo, Uruguay.
The focus of this lecture is to describe how the neural mechanisms that regulate the motivational aspects of maternal behavior and the importance of early maternal/parental-infant interaction.

17:00-17:30 Coffee break

17:30-19:00 Lecture V: *Behavioral influence of maternal separation: Consequences for the mother and the offspring.* **María Angélica Rivarola**, Universidad Nacional de Córdoba, Argentina.
This presentation is aimed at addressing the importance of mother-pup relationships and the consequences of early maternal separation. Neurobiological components involved in this relationship will be discussed.

19:00-20:30 Interactive Activity (VI)
Writing and Publishing
To write and publish is one of the more important instances of the research career. In this activity students will be divided into groups of 6-8 each, and the different professors will be in charged to chair the different topics involve in this matter.

How to prepare a ten minutes talk
One requirement to students for oral presentations at International Meetings is to present all their results in a clear way in a limited period of time. This activity is to point out the most important clues in order to prepare short talks to achieve the best result in communicating science.

20:30-21:00 Discussion Round Table
A final session will be held among students and faculty in order to answer remaining questions related to the subjects covered in the first day of the course.

21.00-22:00 Dinner

Day 2 – Tuesday, October 2nd
Neuroendocrine Mechanisms of Reproduction

08:30-09:30 Breakfast Meeting
A breakfast will be served to students and professors before the first lecture. This seeks to provide students the opportunity to have informal chats with the professors in order to discuss their interests, future plans and career opportunities.

09:30-11:00 Lecture VII: *Principles of neuroendocrine control of reproduction.*
Janete A. Anselmo-Franci
This lecture is intended to provide the students basic knowledge on the neuroendocrine reproductive axis, hormonal cyclicity and how sexual behavior characteristics are under control of neurobiological and hormonal components. This will be required for students to appreciate the subsequent lectures in this section.

11:00-11:30 Coffee break

11:30-13:00 Lecture VIII*: Brain Neuroesteroidogenesis: new regulatory mechanisms of neuroendocrine functions associated with*

reproduction. **Ricardo J. Cabrera**, Instituto de Investigaciones Biomédicas (INBIOMED-IMBECU-CONICET) Universidad de Mendoza, Argentina.
This lecture will demonstrate how sex steroids can influence a great variety of modulatory brain effects which control physiological and pathophysiological behavior and neuroendocrine and metabolic systems related to the reproductive function in males and females.

13:00-14:30 Lunch

15:00-16:30 Lecture IX: *The basics of GnRH neurons.* **Allan Herbison**, Centre for Neuroendocrinology, University of Otago, Dunedin, New Zealand.
This talk will provide an overview of what we know and do not know about the GnRH neurons and the GnRH neuronal network that controls fertility.

16:30-18:00 Lecture X: *Neurobiological mechanisms of puberty onset in higher primates*. **Tony M. Plant**
The neuronal and hormonal control of the prepubertal quiescence in the reproductive axis and the onset of puberty will be considered. The genetic and physiological factors that time infancy and childhood duration will be addressed as well.

18:00–19:30 Lecture XI*: Effects of stress on female reproduction, fertility and mood.* **Janete A. Anselmo-Franci**
During this lecture the close relationship between stress hormones and reproductive function will be considered. Focus will be on the neural systems involved.

19:30–20:30 Round Table
In this part of the course, we will hold the final discussion on the contribution, perspectives and challenges of neuroendocrinology research. Particular emphasis will be given to the problems encountered by young neuroendocrinologists wishing to start a career as an independent researcher. Remaining questions will be taken.

21:00-22:00 Dinner

22.30 Social Event

MEETING PROGRAM

Wednesday, October 3rd

08:00-09:30 Registration

09:30-10:00 Opening

10:00-13:00 Symposium I: Neurobiology of drug addiction: effects in animal models and a translational human.
Chair: Dra. Liliana M Cancela

10:00-10:40 *Dynorphins as modulators of stress and drug addiction: from mice to men*. **Andreas Zimmer**, Institute of Molecular Psychiatry, University of Bonn, Germany.

10:40-11:20 *Repetitive cocaine administration alters GABAergic thalamocortical transmission.*
Francisco J. Urbano, IFIBYNE - CONICET, Universidad de Buenos Aires, Buenos Aires, Argentina.

11:20-11:40 Coffee break

11:40-12: 20 *In vivo visualization of delta opioid receptors upon physiological activation uncovers a distinct internalization profile.* **Dominique Massotte**, Department of Neurobiology and Genetics, IGBMC, Université Paris Descartes, Paris, France.
12:20-13:00 *Stress and vulnerability to develop sensitization to cocaine: a glance at the glutamate system in nucleus accumbens.*
Liliana M Cancela. IFEC-CONICET. Departamento Farmacología, Facultad Ciencias Químicas. Universidad Nacional de Córdoba. Córdoba, Argentina.

13:15-14:30 Lunch

14:30-16:30 Young Investigators Colloquium I

14:30-14:55 *Evolution of the molecular determinants of Calcium Permeability of the Mammalian Hair Cell Nicotinic Acetylcholine Receptor.* **Marcela Lipovsek**, INGEBI – CONICET. Argentina.

15:00-15:25 *Is estradiol treatment a proper strategy for neurodevelopmental disorders associated with perinatal asphyxia?* **Gustavo Ezequiel Saraceno**, Laboratorio de Citoarquitectura y Plasticidad Neuronal, ININCA, UBA-CONICET, Buenos Aires, Argentina.

15:30-15:55 *Dendritic membrane properties influence multimodal integration for fast behavioral decision in the goldfish.* **Violeta Medan**, Facultad de Ciencias Exactas y Naturales, UBA. Argentina.

16:00-16:25 *Astrocyte-astrocyte communication and connexin 43 regulate mammalian circadian rhythms.* **Luciano Marpegan**, Laboratorio de Cronobiologia, Universidad Nacional de Quilmes, Argentina.

16:30-17:00 Coffee break

17:00- 19:30 Poster session I

19:30-20:30 "Hector Maldonado" Lecture
Channelopathies as a source of neurological disorders.
Osvaldo Uchitel, Instituto de Fisiología, Biología Molecular y Neurociencias. IFIBYNE-UBA-CONICET, University of Buenos Aires, Buenos Aires, Argentina.

20:30-21:00: Tasting of wines of TAPIZ Winery

21:00-22:30: Dinner

22:30-24:00 Plenary meeting SAN. SfN local chapter

24:00- Bonfire

Thursday, October 4th

08:30-10:30 Young Investigators Colloquium II

08:30-08:55 *PDF receptor expressing neurons in the ellipsoid body: a link between locomotor and sleep circuits?* **Nicolás Pírez**, Laboratorio de Genética del Comportamiento. Instituto Leloir. Bs. As., Argentina & Dept. of Biology, Brandeis University. Waltham, USA.

09:00-09:25 *Motor coding unveiled by a low dimensional model of birdsong production.* **Ana Amador**, Department of Organismal Biology & Anatomy, University of Chicago, USA & Department of Physics, FCEN, Universidad de Buenos Aires, Argentina.

09:30-09:55 *Phase Coupling between Theta and Gamma Oscillations in the Hippocampus* **Mariano Andrés Belluscio**, Facultad de Medicina – UBA. Argentina.

10:00-10:25 *Consolidating unique memories: BDNF in the dentate gyrus is required for neurogenesis-dependent spatial pattern separation.* **Pedro Alejandro Bekinschtein**, Instituto de Biología Celular y Neurociencia ¨Prof. E. De Robertis¨ (IBCN), Fac. de Medicina, UBA-CONICET. Argentina.

10:30-10:50 Coffee break

11:00-13:00 Poster session II

13:00-14:30 Lunch

14:40-17:40 Symposium II: Vocal Interactions-A dialogue across species.
Chairs: Diego A. Laplagne & **Juan E. Kamienkowski**

14:40-15:20 *HUMANS: Coordination in Human-Human Dialogue.* **Agustín Gravano**, Computer Science Department, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina.

15:20-16:00 *NON-HUMAN PRIMATES: Nonhuman primate communication and the roots of human language*. **Julia Fischer,** Research Group Cognitive Ethology Lab, German Primate Center, Goettingen, Germany.

16:00-16:20 Coffee break

16:20-17:00 *RODENTS: Ultrasonic communication in rodents – Going beyond emotion.* **Diego A Laplagne,** Shelby White and Leon Levy Center for Mind, Brain and Behavior, Rockefeller University, New York, USA.

17:00-17:40 *SONGBIRDS: Wired to cooperate: mechanisms for duet singing in wrens.* **Eric Fortune,** Department of Psychological and Brain Sciences, The Johns Hopkins University, Baltimore, USA.

18:00-19:00 "Ranwell Caputo" Lecture
Deciphering the function of neurotransmitter-gated ion channels: From the molecular to the animal level.
Cecilia Bouzat, INIBIBB-CONICET, Bahía Blanca, Argentina.

19:00-21:00 Poster session III

21:00-22:30 Dinner

23:00- Neuroparty

Friday, October 5th

09:00-11:50 Symposium III: Wnt signalling in nervous system development and functioning
Chair: Silvana Rosso

09:00-09:50 *Rho-GTPase signaling during Axon Formation*
Alfredo Caceres, Instituto Investigación Medica Mercedes y Martín Ferreyra (INIMEC-CONICET)-Universidad Nacional Córdoba, Argentina.

09:50-10:40 *WNT factors trigger neuronal polarization through the activation of IGF-1 receptor / PI3K pathway.* **Silvana Rosso,** Laboratorio de Toxicología Experimental, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Argentina

10:40-11:00 Coffee break

11:00-11:50 *The life and death of the synapse: a role for Wnt signalling.* **Patricia C. Salinas**, Department of Cell and Developmental Biology, University College London, UK.

12:00-13:00 "De Robertis" Lecture
Rethinking glia: their roles in neural circuit formation, plasticity and function
Gabriel Corfas*,* Children´s Hospital, Boston, MA. USA.

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13:15-15:00 Barbecue lunch and farewell

Symposia
ABSTRACTS

<u>Symposium I</u>: Neurobiology of drug addiction: effects in animal models and human studies
Wednesday, 10:00-13:00

<u>Chairman</u>: Liliana M Cancela. E-mail: lcancela@fcq.unc.edu.ar

The main aim of this symposium is to contribute to the discussion of the neurobiological mechanisms of drug addiction. To this end, experimental models in laboratory animals for the different aspects of drug addiction will be covered. It will include generalizations of shared processes with stress (as a precipitating factor of addiction), a glance on the endogenous opioid systems as common biological substrates of different kind of drugs, and the individual characteristics for heroin, cocaine, cannabinoids, and alcohol. The newest molecular, behavioural and electrophysiological advances as well as a translational approach and therapeutic strategies will be proposed for drug addiction.

Dynorphins as modulators of stress and drug addiction: from mice to men
Andreas Zimmer
Institute of Molecular Psychiatry, University of Bonn, Germany

The formation of fear memories and their extinction are necessary for the adaptation to a changing environment. Here with a translational approach we investigated the role of dynorphins in the dynamic change in fear memories in mice and in humans. In mice, genetic deletion of the dynorphin encoding gene Pdyn in mice resulted in enhanced cue-dependent fear conditioning, as well as delayed extinction in contextual and cue conditioning/extinction paradigms. The pharmacological blockade of kappa opioid receptors produced a similar effect on fear extinction as the dynorphin deletion. The behavioral data are supported by the analysis of the induction of the immediate early gene c-fos, which demonstrated that the absence of dynorphin results in reduced neuronal activity in key limbic structures during extinction. Translating these findings into the human domain we could demonstrate that a polymorphism in the dynorphin encoding gene Pdyn impacts the activity of the amygdala, functional coupling between amygdala and the prefrontal cortex and the intensity of stress responses during extinction. Findings on the impact of the dynorphin system on these responses will be also included after THC and alcohol. Our findings establish a role of Pdyn/KOR signaling in fear extinction and suggest a biological mechanism for the success of trauma exposure therapy.

Repetitive cocaine administration alters GABAergic thalamocortical transmission

Francisco J. Urbano
IFIBYNE-CONICET, University of Buenos Aires, Pabellon 2-piso 2, Ciudad Universitaria.

The goal of our lab is to study changes in the intrinsic properties of thalamocortical networks in mice exposed to cocaine. The thalamocortical system is involved in the attentional, perceptual, and sensorimotor deficits present in cocaine abusers, and is, therefore, of direct relevance to the treatment of the deleterious effects of cocaine. However, there is scant precedent of in vitro studies of either intrinsic membrane properties or changes in synaptic transmission across large numbers of thalamocortical neurons in animal models of cocaine intake. A combination of *in vitro* patch-clamp, calcium-dependent dyes imaging and western blotting techniques were used to determine the physiological and molecular mechanisms behind the cocaine-induced over-activation of voltage-gated calcium channels in thalamocortical networks. Acute cocaine exposure induced locomotor activity and GABAergic thalamic alterations. After systemic administration of either T-type calcium channel blockers mibefradil (20 mg/kg) or 2-octanol (0.5 mg/kg and 0.07 mg/kg) cocaine-induced hyperlocomotor activity in vivo as well as GABAergic mini frequencies enhancement onto Ventrobasal (VB) thalamic neurons were prevented. Repetitive administration of cocaine increased changes in GAD65/67 and T-type calcium channels protein levels from VB and Reticular thalamic nuclei. Our results strongly suggest that T-type calcium channels play a key role in cocaine-mediated GABAergic thalamocortical alterations, and further propose that T-type channel blockers might represent potential targets for future pharmacological strategies aimed at treating cocaine's deleterious effects on physiology and behavior.

In vivo visualization of delta opioid receptors upon physiological activation uncovers a distinct internalization profile

Dominique Massotte
Dept of Neurobiology and Genetics, IGBMC, Illkirch.Graffenstaden, Université Paris Descartes, Paris, France.
Faget Lauren1, Erbs Eric1, Le Merrer Julie1, Schrrer Gregory2, Matifas Audrey1, Benturquia Nadia3, Noble Florence3, Decossas Marion4, Koch Marc5, Kessler Pascal5, Vonesch JeanLuc5, Schwab Yannick5, Kieffer Brigitte L.1 and **Massotte Dominique1**
1Department of Neurobiology and Genetics, IGBMC, Illkirch-Graffenstaden, France
2 Department of Physiology and Cellular Biophysics, Columbia University, New York, USA
3 Imaging center, IGBMC, Illkirch-Graffenstaden, France
4 Neuropsychopharmacologie des addictions, Université Paris Descartes, Paris, France.

G protein-coupled receptors (GPCRs) mediate numerous physiological functions and represent prime therapeutic targets. Receptor trafficking upon agonist stimulation is critical for GPCR function, but examining this process in vivo remains a true challenge. Using knock-in mice expressing functional fluorescent delta opioid receptors under the control of the endogenous promoter, we visualized in vivo internalization of this native GPCR upon physiological stimulation. We developed a paradigm in which animals were made dependent to morphine in a drug-paired context. When re-exposed to this context in a drug-free state, mice showed context-dependent withdrawal signs and activation of the hippocampus. Receptor internalization was transiently detected in a subset of CA1 neurons, uncovering regionally restricted opioid peptide release. Importantly, a pool of surface receptors always remained, which contrasts with the in vivo profile previously established for exogenous druginduced internalization. Therefore, a distinct response is observed at the receptor level upon a physiological or pharmacological stimulation. Altogether, direct in vivo GPCR visualization enables mapping receptor stimulation promoted by a behavioral challenge, and represents a powerful approach to study endogenous GPCR physiology.

Stress and vulnerability to develop sensitization to cocaine: a glance at the glutamate system in nucleus accumbens

Liliana M Cancela.
IFEC-CONICET. Departamento Farmacología, Facultad Ciencias Químicas. Universidad Nacional de Córdoba. Córdoba, Argentina.

Stressful life events are thought to promote the development of drug addiction. Impairments in synaptic plasticity in the glutamate projection from the prefrontal cortex to the basal ganglia is a common feature in addiction. including the psychostimulants. Surprisingly, the impairment appears to originate from drug-induced changes in glia and the coupling between glia and neurons in maintaining extracellular glutamate levels. Several evidences indicate that the proactive influence of stress on drug-addiction is exerted on excitatory synapses by the activation of common mechanisms between drugs and stress. This talk will describe the stress-induced impairments in glutamate homeostasis in nucleus accumbens core and shell, and how it influences the responsiveness to cocaine in an animal model of cross-sensitization.

Symposium II: Vocal Interactions-A dialogue across species
Thursday, 14:40-17:40
Chairmen: Diego A. Laplagne, e-mail: dlaplagne@rockefeller.edu
and Juan E. Kamienkowski, e-mail: juank@df.uba.ar.

Across the animal kingdom, individuals produce sounds which, in turn, can be perceived by members of the same species. In this way one can influence the behavior of others, thus establishing a communication channel that can act from short to long distances. In vertebrates the respiratory tract evolved specializations, such as the larynx, that allowed for the controlled coupling of respiration with sound production, giving rise to what we now call "vocal communication". Species within this group share an homologous set of brain structures forming a core system for the production of vocalizations. Sound perception in these species shares as well a large degree of homology, and current research deals with the possibility that this extends into the specific coding of vocalizations. We will explore in this symposium the ethology and neurophysiology of vocal communication between conspecifics. From the exquisitely timed duets of songbirds, to the emotional parallels of rodent ultrasonic calls, the vocal component of rich social behavior in primates and the complex linguistic interactions of human dialogues. By probing what is common and what is distinct between these implementations we aim at achieving a better understanding of the evolution of vocal communication and, perhaps, of that still mysterious leap into full fledged human language.

Coordination in Human-Human Dialogue

Agustín Gravano
Computer Science Department, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina.

Spoken interactions between humans are typically characterized by a high degree of coordination, with participants smoothly alternating their contributions to exchange information in an efficient manner. Needless to say, there are multiple factors that allow for such a coordinated communication; and these many factors are part of the reason why computers with the ability to converse naturally with humans still remain a science-fiction topic. In this talk I will discuss two complex phenomena that facilitate human-human dialogue. First, I will present a model of 'turn-taking cues' -- acoustic, prosodic, lexical and syntactic events produced by speakers that alert their interlocutors whether they may or may not take the next conversational turn. I will also describe a series of studies on 'speaker entrainment', showing that dialogue partners often become more similar to each other, a phenomenon that has been found to occur along many dimensions of human communication, and has been associated with dialogue success and naturalness. I will finish by outlining some possible directions for cross-species studies.

Nonhuman primate communication and the roots of human language

Julia Fischer
Cognitive Ethology Lab, German Primate Center, Göttingen

I will explore the commonalities and differences in the vocal communication of nonhuman primates and humans. Research in the last decades has yielded strong evidence in favor of the assumption that the acoustic structure of nonhuman primate vocalizations is largely innate, with only limited plasticity. On the other hand, nonhuman primates exhibit considerable flexibility in terms of the comprehension of calls and the integration of information from different sources. I will present a number of studies that addressed the question of adaptation to the habitat, the importance of phylogenetic relationships, and physiological effects on call production. Further, I will present a recent model of the cognitive mechanisms supporting flexible responses and decision making. In addition, I will briefly discuss the issue of lateralized processing of sounds, a hallmark in human speech perception. Taken together, the findings suggest that evolutionary constraints played an important role in the evolution of primate communication, while the ability to learn and integrate information made up for some of the restrictions in vocal production. Whether or not further studies of nonhuman primate communication will indeed solve the puzzle of the origin of speech remains an open issue.

Ultrasonic communication in rodents – Going beyond emotion

Diego A Laplagne
Shelby White and Leon Levy Center for Mind, Brain and Behavior
Rockefeller University, New York, USA

Rats and mice produce vocalizations that span the frequency range from the sonic to the ultrasonic. Sonic calls are scarce and produced only in extreme scenarios like predator encounters. In the rat, emission of prolonged 22 kHz calls correlates with aversive and fearful conditions and has been shown to convey alert to listeners. Above 40 kHz, rats produce a rich repertoire of vocalizations spanning a wide range of frequency, frequency modulation and duration. Semantic studies on these ultrasonic vocalizations (USVs) have shown a correlation with positive situations like satiety, reward and social interaction, although the fine semantics of call types within this family remains elusive. Current knowledge thus supports a clear link between vocal production and emotional state in the rat. Do calls only broadcast an individual's current state or does vocal communication in the rat support other behaviors? On the syntax side, few studies have shown that mice can sequence USVs in neither random nor completely stereotyped motifs, but syntax and temporal structuring remains largely unexplored in rats. Furthermore, despite the social role of vocal communication, no study has analyzed the dynamics of vocal interactions between rodents, mainly due to the difficulty of assigning calls to individuals in a common acoustical environment.

We have developed a setup for recording and assigning calls from pairs of rats. Automated analysis and classification leads to high volume datasets suitable for syntactic analysis within and across rats. By simultaneously measuring nasal airflow we have shown how breathing patterns shape the temporal structure of vocal production and segment it in 'calls'. In term, call autocorrelations suggest the existence of new meaningful USV subclasses, with some of these displaying interesting interactions between individuals. To directly address the possibility that call production goes beyond emotional control we are probing the ability of rats to use calls as responses in operant behaviors. Vocalizing is ultimately a motor gesture. Should it be found amenable to operant conditioning that would prove rats have equivalent volitional control of it as of others such as those required for locomotion or lever-pressing.

Wired to cooperate: mechanisms for duet singing in wrens

Eric Fortune
Department of Psychological and Brain Sciences, The Johns Hopkins University, Baltimore, USA

Cooperative behaviors, such as dancing the tango, require precise coordination of learned movements between individuals. To achieve these performances, brain circuits in each participant must integrate of information from at least two sources, feedback from the animal's own behavior and information from the partner. How the brain represents these categories of sensory information for the production of these cooperative behaviors is currently not known in any species. Here we show that telencephalic neurons in a song control area 'HVC' of plain-tailed wrens (Pheugopedius euophrys) represent the combined cooperative behavior, a duet song in which females and males alternate syllable production, rather than each individual's motor contributions to the duet. HVC neurons responded best to playbacks of the duet song over all other stimuli tested in neurophysiological recordings achieved in urethane anesthetized female and male wrens. In most neurons, the playback of the female components alone elicited strong responses, even in male birds that never produce the female syllables.
Further, these neurons were sensitive to the intervals between syllables, which in duet singing is when the other bird sings its contributions, and is also a correlate of solitary singing in these birds. These data demonstrate that neurons in the brains of individual participants can encode the combined outcome of a cooperative behavior.

<u>Symposium III:</u> Wnt signalling in nervous system development and functioning

Friday, 09:00-12:00

<u>Chairman</u>: Silvana Rosso. E-mail: srosso@fbioyf.unr.edu.ar sbrosso@gmail.com

Wnts factors comprise a family of secreted glycolipoproteins able to interact with cell surface receptors eliciting a variety of intracellular responses. To date, 19 distinct Wnts have been identified in mammals. The diversity of the Wnt expression is highly conserved among animal species. Wnts can signal through different receptors including Frizzled family, the LRP5/6 coreceptors, and the tyrosine-kinase receptors as ROR2 and RYK. Binding of Wnts to their receptors activates a number of intracellular cascades: the Canonical Pathway, in which Wnt-receptor interaction activates the scaffolding protein Dishevelled (Dvl), which inhibits a complex formed by Axin, APC, and GSK3β. The event leads the stabilization and translocation of β-Catenin into the nucleus, where it associates with the transcription factor TCF/LEF to regulate Wnt target genes. The Planar Cell Polarity pathway (PCP), which involves the activation of small Rho-GTPases and kinases that modulate the actin and microtubule cytoskeleton and the Wnt/Calcium Pathway, which involves the regulation of intracellular levels of calcium plus the activation of Ca+2-sensitive kinases. Wnt signalling is crucial in embryonic development, from gastrulation and early pattern formation to organogenesis, and in adult organisms, where it plays a central role in the maintenance of tissue homeostasis. Wnt signalling controls diverse processes, such as cell proliferation, self-renewal, cell polarity, cell death and cell fate specification. Particularly, during nervous system development, Wnt signalling is essential to regulate morphological complexity of neurons and functioning. Wnts can also function as morphogens, acting in both short- and long-range signaling, modulating target cells in a dose and distance-dependent manner. Wnts play a key role during early developmental processes such as neurogenesis, axon outgrowth, neuronal polarization, dendrite formation and synapses. Moreover, their high expression in mature neurons suggests the involvement of Wnt signalling in synaptic maintenance and function. Regulation of cell signalling by Wnt proteins is critical for the formation of neuronal circuits. Thus, there are evidences suggesting that dysfunction in Wnt signalling may contribute to neurological disorders.

Rho-GTPase signaling during Axon Formation

Alfredo Caceres, José Wojnacki and Gonzalo Quassollo
Instituto Investigación Medica Mercedes y Martín Ferreyra (INIMEC-CONICET)-Universidad Nacional Córdoba, Argentina.

It is now clearly established that the highly dynamic remodeling and cross talk of the microtubule and actin cytoskeleton support axon formation and neuronal polarity. Small Rho-GTPases family members have emerged as crucial regulators of cytoskeletal dynamics and microtubule and actin filament crosstalk. Using a combination of cell and molecular biology techniques, including imaging with FRET biosensors for RhoA, Rac and Cdc42, we now show that a pathway involving Lfc-RhoA and Rho Kinase, negatively regulate initial neurite formation, as well as axon specification and outgrowth. This pathway is counterbalanced by Tctex-1, a dynein light chain, which negatively regulates Lfc to promote axon formation. Interestingly, after polarization, RhoA has a stimulatory effect on axon elongation that involves the formin mDia. Together our observations suggest that depending on the context and stage of differentiation RhoA can act as a positive or negative regulator of axonal growth.
Supported by ANPCyT (Argentina), CONICET (Argentina) and Agencia Cordoba Ciencia.

WNT factors trigger neuronal polarization through the activation of IGF-1 receptor/ PI3K pathway

Silvana B. Rosso
CIQUIBIC-CONICET. Facultad de Ciencias Químicas, Universidad Nacional de Córdoba. Argentina. *Present Address: Laboratorio de Toxicología Experimental, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Argentina

During nervous system development, Wnt signalling is essential to regulate morphological complexity of neurons and functioning. Wnts factors are crucial for early developmental processes such as neurogenesis, axon outgrowth, axon guidance, neuronal polarization, dendrite formation and synapses. Previously, we demonstrate that Wnt-Dishevelled regulates neuronal maturation, particularly dendrite formation and complexity through a signaling pathway involving Rac and JNK. Consistent with these findings, hippocampal neurons from Dvl1 mutant mice exhibit reduced dendritic arborization and dominant-negative forms of Rac or JNK block Dvl-mediated dendritic growth. However, little is known about the role of WNT signalling earlier, particularly on the initial axonal outgrowth and the establishment of neuronal polarity.

Neuronal polarization requires polarized activation of IGF-1 receptors by insulin or IGF-1 and subsequent activation of the PI3k pathway. Although, Wnt factors have been also implied in the regulation of axonal development it is not known whether Wnts participate in the regulation of initial axonal outgrowth and the establishment of neuronal polarity. Our experiments show that stimulation of hippocampal neurons with Wnt3a factor is sufficient to trigger neuronal polarization in the absence of IGF-1 or a high level of insulin. Furthermore, Wnt3a triggers the activation of IGF-1 receptors and PI3k (polarized to one minor neurite) in undifferentiated neurons (stage 2) and also in growth cone particles (GCPs). In addition, we show that the presence of activate IGF-1 receptors and PI3k activation are necessary for Wnt3a polarizing effects. Finally, using binding and immunoprecipitation experiments, we show that Wnt3a binds to IGF-1 receptors. We conclude that Wnt3a triggers polarization of hippocampal neurons via activation of the IGF-1 receptor/PI3k pathway. These findings suggest a possible parallelism between the two signalling systems: Wnt-Fz-DVL and IGF-1-IGF receptor-PI3K on axon formation.

We conclude that the Wnt-DVL pathway is essential for neuronal development from axon formation to dendrite maturation by activating different secondary signalling cascades.

Supported by FONCYT, SECYT Córdoba, MINCyT Córdoba

The life and death of the synapse: a role for Wnt signaling

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My laboratory has been studying the mechanisms that regulate the formation, growth and function of synapses. We found that Wnt secreted proteins promotes the formation of central and peripheral synapses. More recently we have focused our studies in understanding the mechanisms by which Wnts promotes the formation and growth of dendritic spines and synaptic strength. I will discuss our recent studies that demonstrate that local activation of the Wnt signalling pathway promotes both spine growth and synaptic strength of excitatory synapses.

Another major focus of our lab is studying the role of Wnt signaling in the maintenance of synapses in the adult brain and its contribution to synaptic degeneration in Alzheimer's disease. Although in the adult brain most synapses are stable, very little is known about the mechanisms that control synaptic stability. Importantly, the loss of synapses in Alzheimer's disease (AD) is correlated with cognitive decline. Extensive evidence supports a central role for Amyloid-ß (Aß) in the pathogenesis of AD. Indeed, synaptic loss mediated by Aß in early stages of the disease might contribute to cognitive impairments. However, little is known about the mechanism by which Aß induces the loss of synapses. The Wnt antagonist Dickkopf-1 (Dkk1) is increased in brains of AD patients and of transgenic mouse models, suggesting that Dkk1 might contribute to AD pathology. Here we report that Aß rapidly induces Dkk1 expression together with the loss of synaptic sites. Importantly, Dkk1 neutralizing antibodies suppress Aß-induced synapse loss in mouse brain slices. In hippocampal neurons, Dkk1 reduces the number of synapses without affecting cell viability. Our studies demonstrate a novel role for Wnt signaling in the maintenance of synapses in mature neurons and identify Dkk1 as a potential therapeutic target for the treatment of AD.

Our work is funded by the MRC, the Wellcome Trust, the BBSRC, Alzheimer's Research UK and the EU F7.

Plenary Lectures
ABSTRACTS

"Hector Maldonado" Lecture
Wednesday, 19:30-20:30

Channelopathies as a source of neurological disorders

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During the past two decades it has become apparent that diseases once thought unrelated share alterations in the regulation of ion channels. Ion channels regulate neuronal and muscular excitability. Alterations in their function could result in conditions such as periodic paralysis, epilepsy and migraines. In these cases, the result of neurobiological research has led to the conclusion that the underlying cause is a channelopathy, which has served as guide for the development of therapies to treat these diseases. By way of example, many antiepileptic drugs block the sodium channel or the activation of ligand-dependent receptors. Migraine is one of the most common neurological conditions. However, there is a rarer form of migraine, the so called familial hemiplegic, which is accompanied by hemiparesis, and has a monogenic origin related to mutations of the P / Q calcium channel. The generation of transgenic mice with different human mutations (knock in) allowed the study, in their normal cellular environment and under their natural regulation, of the expression of the mutated channel and their effects on synaptic transmission. It has also made possible the detailed investigation on the effect of potential therapeutic agents. The results of these studies show that, at the synaptic level, the phenotypic expression of the mutation depends particularly on the kinetic properties of the action potential of neurons, generating a gain increase in the excitatory neurons but not in the inhibitory ones. This disparity leads to an imbalance between excitation and inhibition that could be the basis of the cortical hyperexcitability observed both in patients and in animal models. This phenomenon has been interpreted as the starting point of the aura, which precedes the migraine attack.

"Ranwell Caputo" Lecture

Thursday, 18:00-19:00

Deciphering the function of neurotransmitter-gated ion channels: From the molecular to the animal level

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Pentameric neurotransmitter-gated ion channels mediate rapid communication in the nervous system, and include nicotinic (AChR), GABA, glycine and 5-HT3A receptors. They are implicated in important physiological functions, in neurological disorders and they are targets of therapeutic drugs. Receptors are also present in non-neuronal cells and are highly conserved in nematodes, where they are targets of antiparasitic drugs. By combining mutagenesis, cell-expression, patch-clamp recordings and in silico studies we identified key regions involved in the functional connection between agonist binding and channel opening and we defined sites and mechanisms of drugs affecting receptor activation. This information provides a foundation for the understanding of synaptic responses and their modulation. We determined that lymphocytes have neuronal-like synaptic components and express GABAA and neuronal □7 AChRs, which emerge as potential targets for modulating the immune response. We deciphered the composition of C. elegans muscle AChRs and generated transgenic worms carrying mutations in muscle AChR subunits, which mimic those found in patients suffering from congenital myasthenic syndromes (CMS). We postulate that C. elegans is a valid model for studying human CMSs and for drug screening.

"De Robertis" Lecture
Friday 12:00-13:00

Rethinking glia: their roles in neural circuit formation, plasticity and function

Gabriel Corfas
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Glial cells were considered, for a long time, to be primarily connective Tissue for the nervous system. However, in recent years it has become evident that glia play key active roles in many aspects of nervous system development, function and maintenance. In this lecture I will discuss our findings on the roles of glial cells in the formation, function and plasticity of neural circuits, the impact of glial cell dysfunction on behavior and some of the molecules that mediate neuron-glia interactions.

Young Investigators Colloquia
ABSTRACTS

Young Investigators Colloquium I
Wednesday, 14:30-16:30

Evolution of the molecular determinants of Calcium Permeability of the Mammalian Hair Cell Nicotinic Acetylcholine Receptor

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The α9α10 cholinergic nicotinic receptor (nAChR) mediates efferent inhibition of inner ear hair cells, a mechanism thought to modulate the dynamic range of hearing. The Ca2+ permeability of the mammalian α9α10 nAChR is among the highest reported for a ligand-gated ion channel (PCa/PNa~10), in accordance with its known function as the source of Ca2+ entry to cochlear hair cells (Elgoyhen et al, 2001). Surprisingly, we now report that the Ca2+ permeability of the chicken α9α10 nAChR (PCa/PNa<2) is much lower than that of its mammalian counterpart (Lipovsek et al, 2012). This may follow from the differential evolutionary history recently described for vertebrate α9α10 nAChRs (Franchini and Elgoyhen, 2006) and provides the opportunity to analyze the determinants of Ca2+ permeability that natural selection (and not arbitrary experimental mutagenesis) has fixed. Through the generation of mutant and chimeric receptors we identified such determinants in the extracellular vestibule and the TM1-TM2 loop. These results support recent findings showing that ions are selected along the entire conduction pathway. In addition, they suggest that high Ca2+ permeability of the α9α10 nAChR might have evolved together with other features rendering mammals with an expanded high frequency sensitivity.

Is estradiol treatment a proper strategy for neurodevelopmental disorders associated with perinatal asphyxia?

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Even though neurodevelopmental disorders (NDDs) are known to begin before birth, some of them manifest afterwards. Perinatal asphyxia (PA) is an important risk factor for several NDDs since it affects the accurate establishment of neural circuits during a period of apparent normal development. We address the evolution of the damage in CA1 hippocampal area induced by PA in rats using different cytoskeleton markers associated with NDDs. At 30 days of age we observed increased spinogenesis, augmented number of mushroom-type dendritic spines (MDS) and higher β-actin mRNA and protein levels. At 120 days of age we found reactive gliosis, dendritic morphological alterations, increased phosphorylation status of neurofilaments, decreased MDS and increased thickness of postsynaptic densities. Regarding these results, we employed an estradiol treatment (250ug/kg, 3 days) whereby the long term alterations induced by PA were reversed through the activation of the ERα/IGF-IR signaling pathway. These results support our working hypothesis that PA induces age-dependent alterations in synaptic connectivity before the establishment of symptoms associated with NDDs. Moreover, ERα/IGF-IR signaling pathway may represent a therapeutic target for the treatment of PA-induced neurological alterations.

Dendritic membrane properties influence multimodal integration for fast behavioral decision in the goldfish

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Animals integrate information from different sensory modalities to form percepts that allows adaptive behavioral decisions. Great advances have been made by studying sense organs one at-the-time. However, understanding of multimodal integration and its role in decision-making has lagged behind. Our goal is to extend our knowledge about the contribution of single neurons in multimodal integration. Specifically, we try to understand basic but essential phenomena as how neurons process multimodal sensory input with variable temporal dynamics and if dendrites show specific adaptations according to their input sensory modality. These questions are typically studied in vitro or in silico. We use however, an in vivo model system, the Mauthner cell (M-cell) circuit, responsible of triggering the escape response of the goldfish (Carassiusauratus) combined with biologically relevant stimuli. Interestingly, the M-cell receives anatomically segregated visual and auditory inputs. We found that the M-cell integrates visual and auditory stimuli of remarkably different temporal characteristics (abrupt auditory pips and visual looms) in a nonlinear fashion. Moreover, the differences in the electrical and morphological properties of its dendrites influence this nonlinear integration.

Astrocyte-astrocyte communication and connexin 43 regulate mammalian circadian rhythms

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Evidence from in vivo and in vitro studies indicates that intercellular communication modulates the rhythmic physiology in mammals. Glial cell activity has been implicated, but understudied, in the circadian system. We showed previously that astroglia are competent circadian oscillators which synchronize to diffusible signals from the SCN and that vasoactive intestinal polypeptide (VIP) can coordinate rhythms in astrocytes. Here, we studied the effects of cell-cell interactions on circadian timing in cultured astrocytes. Measuring PER2::LUC bioluminescence rhythms from cultured, mouse cortical astrocytes we found that astrocytes plated at high density (1200 cells/mm2) displayed longer periods and faster damping rates than low density cultures (100 cells/mm2; 24.7±0.1 vs. 25.9±0.1 h, p< 0.01). These period and damping rate differences were preserved when astrocytes at high density were cultured next to astrocytes at low density, leading us to hypothesize that glia can modulate circadian timing in neighboring glia. Since gap junctions can mediate short-range interactions between astrocytes, we tested the effects of gap junction blockers in astrocyte cultures and SCN explants. Meclofenamic acid (MEC, 150□M) increased the damping rate in both high and low density astroglia and decreased the period in high density cultures (25.4±0.1h to 23.6±0.3h, p<0.05). Addition of 50□M MEC to SCN explants also shortened the period and damped PER2::LUC rhythms. Similar results were observed with Carbenoxolone (200□M), another potent gap junction blocker. Using immunocytochemistry and Western blots, we found connexin 43, the major component of gap junctions in astrocytes, was circadian in cultured cortical astrocytes and *in vivo*. Taken together these results suggest that intercellular communication among astrocytes via gap junctions, modulates the period and sustainability of the circadian clock.

Young Investigators Colloquium II
Thursday, 08:30-10:30

PDF receptor expressing neurons in the ellipsoid body: a link between locomotor and sleep circuits?

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The peptide PDF is an important regulator of the circadian clock in insects. *pdfR*-GAL4 drives expression in ellipsoid body (EB) cells, a component of the central complex. This suggests that the EB may provide an important link between the clock and sleep/activity circuits. How the circadian clock and sleep deprivation might affect the activity of this group of neuronswas unknown. To approach this issue, we performed whole brain optical imaging experiments using flies that expressa FRET-based cAMP sensor under the control of the *pdfR* promoter. Basal cAMP levels were insensitive to time of day and to 1 µM TTX, but were reduced by mutation of the *pdfR* gene.Bath application of PDF caused a significant change in the cAMP level of EB cells which was blocked by mutation of the *pdfR* gene.ACh was found to cause a significant increase in cAMP levels, which had both direct and indirectcomponents,implying thatACh is able to stimulate inputs to EB during the day that increases cAMP.To test the effect of sleep deprivation (SD), we sleep deprived the flies for 12h prior to imaging. Although the effect of SD is clear at the behavioral level, the cAMP responses of these cells to either PDF or AChremained similar to non-SD controls, suggesting that cyclase coupling is not modulated by SD.

Motor coding unveiled by a low dimensional model of birdsong production

Ana Amador[1, 2], Yonatan Sanz Perl[2], Gabriel B. Mindlin[2] and Daniel Margoliash[1]

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Songbirds are a well studied example of vocal learning and motor control that allows to integrate neural and peripheral recordings with a precisely quantifiable behavior. We worked with a minimal physical model for birdsong production. To validate this model, we assessed the responses in the premotor forebrain nucleus HVC to song playback in which neurons exhibit highly selective responses to the bird's own song (BOS). Remarkably, the mathematical model elicited responses strikingly similar to those for BOS, with the same phasic-tonic features. These results demonstrate that a low dimensional model is sufficient to capture behaviorally relevant features, providing valuable simplification that can help clarify neural coding. Analyzing HVC neurons responses to playback of each bird's own song, we observed that projection neurons were excited and interneurons were suppressed, with near-zero time lag, at particular events of the song unveiled by the mathematical model. In preliminary data, we confirmed these results with HVC recordings in singing birds. Given that HVC activity occurs with near synchrony to behavioral output, we propose that the activity of HVC neurons represents the sequence of particular events in song as a "forward" model making predictions on expected behavior.

Phase Coupling between Theta and Gamma Oscillations in the Hippocampus

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Neuronal oscillations allow for temporal segmentation of neuronal spikes. Interdependent oscillators can integrate multiple layers of information. We examined phase–phase coupling of theta and gamma oscillators in the CA1 region of rat hippocampus during maze exploration and rapid eye movement sleep. Hippocampal theta waves were asymmetric, and estimation of the spatial position of the animal was improved by identifying the waveform-based phase of spiking, compared to traditional methods used for phase estimation. Using the waveform-based theta phase, three distinct gamma bands were identified: slow gammaS (gammaS ; 30–50 Hz), midfrequency gammaM (gammaM ; 50–90 Hz), and fast gammaF (gammaF ; 90–150 Hz or epsilon band). The amplitude of each sub-band was modulated by the theta phase. In addition, we found reliable phase–phase coupling between theta and both gammaS and gammaM but not gammaF oscillators. We suggest that cross-frequency phase coupling can support multiple time-scale control of neuronal spikes within and across structures.

Consolidating unique memories: BDNF in the dentate gyrus is required for neurogenesis-dependent spatial pattern separation

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Successful memory involves not only remembering information over time, but also keeping memories distinct and less confusable. The computational process for making representations for similar input patterns more distinct from each other has been referred to as 'pattern separation'. Although adult-born immature neurons have been implicated in this process, information on how they would perform pattern separation and their particular role in memory storage is unclear. In this work, we developed a set of behavioural conditions that allowed us to manipulate the load for pattern separation at different stages of memory. Thus, in this work, we provide the first experimental evidence that a BDNF-dependent pattern separation process occurs during the encoding/storage/consolidation, but not the retrieval stage of memory processing. We also found that a spontaneous increase in BDNF in the dentate gyrus of the hippocampus is associated with exposure to landmarks delineating similar, but not dissimilar spatial locations, suggesting that BDNF is expressed on an "as-needed" basis for pattern separation. Infusion of BDNF into the dentate gyrus was able to enhance pattern separation and this effect was mediated by NMDA glutamate receptors and adult-born immature neurons, indicating a role for these cells in memory consolidation of "pattern separated" memories in the DG.

Poster
ABSTRACTS

Cellular and Molecular Neurobiology
Poster Number 1 / Session I

Melanocortin receptor type 4 (MC4) differentially modulates neuronal voltage operated calcium channels (VOCCs) subtypes

Francina Agosti, Eduardo Javier López Soto, Silvia Rodríguez, Mario Perello, Jesica Raingo

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MC4 is a G protein coupled receptor highly expressed in neurons involved in appetite control. MC4 mutations are, by far, the most common cause of monogenic obesity in humans. MC4 activity impacts in many aspects of neuron function, including synaptic activity. Moreover, MC4 exhibits basal activity. Presynaptic neuronal VOCCs control neurosecretion. Two different genes encode presynaptic VOCCs CaV2.1 and CaV2.2. These channels are highly sensitive to G protein coupled receptors mediated modulation. Here, we investigated how MC4 basal and evoked activity impact on CaV2.1 and CaV2.2 function. We used the patch clamp technique in transfected HEK293 cells co-expressing CaV2.1 or CaV2.2, the auxiliary subunits of calcium channels and the MC4. We found that MC4 co-expression reduced CaV2.1 basal calcium currents while it did not alter CaV2.2 basal current levels. When we applied the MC agonist MTII to HEK293 cells co-expressing CaV2.2 and MC4, we found a concentration dependent inhibitory effect on CaV2.2 currents. When we evaluated MTII effect on 5 cells co-expressing CaV2.1 and MC4 that displayed calcium currents we found no effect of MTII. Our results suggest that MC4 activity would have a differential effect on the two major presynaptic calcium channels: CaV2.1 is inhibited by basal MC4 activity and CaV2.2 is sensitive to agonist-evoked MC4 activity. We are now investigating these two separated pathways in terms of the G protein and second messengers involved.

Cellular and Molecular Neurobiology
Poster Number 2 / Session II

Expression of GluN1 and GluN2A subunits of NMDA receptor increases after KCl depolarization of cultured neurons from rat hippocampus

Alejandra Inés Aguirre [3, 1], Magalí Cecilia Cercato [3], María Verónica Baez [3, 2], Diana Alicia Jerusalinsky [3, 1, 2]

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NMDA receptors (NMDAR) are tetramers containing two GluN1 and two variable regulatory subunits which determine some functional properties. In rat hippocampus major regulatory subunits are GluN2A and GluN2B. Our recent results show that in rat hippocampus, GluN1 and GluN2A, though not GluN2B levels, are significantly higher at 70 min, but not at 30 min following a 5 min open field session (Snitcofsky et al.). Similar changes took place after LTP induction in hippocampal slices (Cercato et al.). To investigate where are these changes expressed, primary cultures of rat hippocampal neurons were stimulated with pulses of KCl to induce LTP-like plasticity (Wu et al., 2001); the subunits were assessed by immunocytochemistry 0, 30 and 70 min after KCl . LTP-induced increase of NMDAR puncta, as reported by Barria and Malinow in hippocampal slices (2002), was verified in dendritic spines 30 min after KCl stimulation, while total immunofluorescence did not change. This could be due to transport along the membrane from extrasynaptic sites and/or delivery from subsynaptic pools. However, 70 minutes after KCl stimulation an increase in total immunofluorescence, as well as in the number of spines expressing GluN1 and GluN2A, was evidenced. No changes were observed for GluN2B. These results are in agreement with those we obtained from electrophysiological and behavioral assays, strongly supporting the possibility that these changes are actually expressed in NMDAR at the synapses.

Cellular and Molecular Neurobiology
Poster Number 3 / Session III

Activity-dependent neuronal maturation in the adult hippocampus

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The adult dentate gyrus contains neural stem cells that generate neurons that develop and mature during several weeks. We have recently demonstrated that the rate of neuronal maturation is regulated by electrical activity in the local circuit; more active networks promote faster maturation rates. To investigate whether developing neurons display a critical period for their sensitivity to electrical activity we now tested how increased neuronal activity by running during restricted time windows modulate neuronal maturation. Preliminary data shows that developing neurons display a high sensitivity to network activity during the initial stages of maturation (before 11 days). To test the role of intrinsic activity on neuronal maturation we performed retroviral expression of RASSLs (receptor activated solely by synthetic ligands) that can activate (HM3D) or silence (HM4D) newborn neurons. We have showed that new neurons expressing HM3D increased ARC expression in response to oral or intraperitoneal administration of the ligand CNO, indicating that adult-born neurons can be activated in vivo with this tool. We have now started a set of experiments to perform chronic manipulations of intrinsic neuronal activity to assess the effects on maturation. Data analysis is underway.

Cellular and Molecular Neurobiology
Poster Number 4 / Session I

Characterization of the polyglutamine domains of Piccolo and Bassoon presynaptic proteins: potential determinants for protein recruitment to the presynaptic active zone.

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Piccolo and Bassoon, two related proteins multidomain family proteins are known scaffold proteins crucial for the formation of the presynaptic active zone. The function of these molecules in the synapse is poorly known as the mechanism of their recruitment to the synapse. We have identified domains of poly-glutamine (Poly-Q) into Piccolo (Poly-Q 1, 2 and 3) and Bassoon (Poly-Q 1 and 2), some of which are very similar to poly-Q domain of the CPEB dendritic protein of Aplysia californica, which has been shown to have prion-like behavior and aggregation has been suggested to be important for its function. We hypothesize that these domains show similar aggregation properties to CPEB and the clustering of these molecules may result in a mechanism of molecular trapping of these proteins to the synapse. Here we evaluate the ability of aggregation and distribution of Piccolo and Bassoon Poly-Q domains in different heterologous cell lines (HEK, COS-7 and insulinoma) and their distribution in primary cultures of hippocampal neurons to 5, 7 and 15 div. Heterologous cells showed different levels of aggregation as well as a nuclear localization domains 2, 3 and Piccolo 1, 2 Bassoon. In neurons showed a nuclear localization and juxtanuclear and is also found at growth cones. The aggregation of these domains suggest that these motifs could be important for their recruitment to active zones. Funded by Fondecyt 1110944

Cellular and Molecular Neurobiology

Poster Number 5 / Session II

Characterization of M4 muscarinic acetylcholine receptor homo- and hetero-oligomerization by bioluminescence resonance energy transfer in live cells

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Recent data suggest that M4 muscarinic acetylcholine receptors (M4R) form constitutive homo-oligomers. This study used bioluminescence resonance energy transfer (BRET) to assess the ability of M4R to form homo- and hetero-oligomers in live HEK 293 cells. Cotransfection of cells with a fixed amount of Renilla Luciferase-tagged M4R and increasing amounts of YFP-tagged M4R resulted in a gradual increase in BRET upon addition of coelenterazine h. The resulting saturation curve could be fitted into a hyperbolic function, indicating that M4R can interact with one another to form constitutive homo-oligomers (BRETmax: 93,9 ± 0.4 mB; BRET50: 1.4 ± 0.2). Quantitative BRET analysis revealed that the M4R population is predominantly composed of high affinity homodimers (84%). BRET saturation curves showed that M4R can also interact with other muscarinic receptor subtypes like M2 and M3 to form hetero-oligomers, but not with the distantly related seven transmembrane receptor Smoothened. Short-term agonist exposure (Carbachol, 10 µM, 5-30 min) did not significantly modify the oligomeric status of M4R-M4R interaction. These data reveal new pharmacological properties of M4R and encourage future research to elucidate the role of oligomerization in muscarinic receptor pharmacology

Cellular and Molecular Neurobiology
Poster Number 6 / Session III

Subcellular localization of CLP36 protein in chicken retina

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CLP36 (PDLIM 1-3) is a protein member of the PDZ-LIM family that has 4 functional domains:a PDZ domain at the N-terminal,1-3 LIM domains at the C-terminalwhichinteracts to the actin cytoskeleton; aZASP-like domain that interacts with α-actinin(an actin-crosslinking protein) and ALP-like domain that interacts with protein kinases. It is known that the signaling pathway PDZ-LIM family proteins involve only the LIM domain and that PDZ domain is related to the anchored properties of this protein. There is little information about the role of CLP36 in central nervous systemand retina. The present study describes the immunohistochemistry localization of CLP36 in the chick retina and also we analyzed subcellular fractionation by western blot. Using an antibody which detects CLP36 we have observed that only the synaptic endings of double cones are stained. Subcellular fractionation showed that CLP36 is present at the 0.9M fraction (synaptosomes). Results allowed us to argue that CLP36 could serveas a scaffoldof molecular complex and could be involvedin the synaptic structure, making functional organization with actin. Our observations in chick retina rise new questions about the regulatory pathways of CLP36 protein and its potential role in synaptic plasticity in chick retina. PIP00404.

Cellular and Molecular Neurobiology
Poster Number 7 / Session I

Recruitment of arrestin-2 to activated M2 muscarinic acetylcholine receptors. Roles of G protein-coupled receptor kinase 2 and Giα protein

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Previous studies have explored the role of phosphorylation and arrestin (Arr) binding in M2 muscarinic acetylcholine receptor (M2R) desensitization and internalization. Here we studied the influence of G protein-coupled receptor kinase 2 (GRK2) and Giα protein (Giα) on the interaction between M2R and Arr-2 by bioluminescence resonance energy transfer (BRET). Titration assays on HEK 293 cells expressing various proportions of M2-RLuc and Arr-2-YFP demonstrated that agonist exposure (carbachol, 10 µM, 20 min) promotes the interaction between M2R and Arr-2 only in the presence of overexpressing GRK2. Agonist-mediated effects were time- and concentration-dependent (t1/2: 2.2 min, Emax: 26.1 mB, EC50: 2.2 µM). Cellular overexpression of kinase-deficient mutant GRK2K220R prevented agonist-induced Arr-2 recruitment to the M2R, suggesting that this effect is mediated by receptor phosphorylation. Coexpression of increasing amounts of Giα promoted a gradual decrease in agonist-mediated Arr-2 binding to M2R, supporting the classical notion that Gα proteins and arrestins compete for binding to activated G-protein coupled receptors. We conclude that agonist-induced Arr-2 binding to the M2R requires receptor phosphorylation and that this effect is affected by the cellular complement of Giα.

Cellular and Molecular Neurobiology
Poster Number 8 / Session II

Looking for orsai's genetic partners in the Drosophila eye

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As a result of a missexpression screen carried out in our lab a mutant was found that could be involved in neurodegeneration. In the original screen, randomly generated mutants expressing the affected gene(s) specifically in the pdf circuit, the fly central pacemaker, were tested in locomotor activity assays. We selected mutants that display rhythmic activity when young but arrhythmicity as they age. A mutation that affected an unknown gene, CG6115, was selected for in depth analysis. Homozygous larvae do not develop further than second instar and finally die. These mutant larvae show no interest for food. Taking into account this phenotype in which the larvae are found where they are not expected to be (i.e., outside the food source) CG6115 was named orsai. To assert orsai's genetic partners, an enhancer/suppressor screen is being carried out using the fly eye. A collection of small chromosome deletions is combined with orsai RNAi expressed in the eye. The RNAi per se shows a rough eye phenotype, which could be rescued (improved) or made worse in the absence of additional proteins required for its function. So far the second chromosome has been completely screened. Most deletions affected genes involved in response to starvation, muscle development and response to oxidative stress.

Cellular and Molecular Neurobiology
Poster Number 9 / Session III

Defective pruning of hippocampal projections in mouse models of Mecp2 dysfunction

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Methyl Cytosine Binding Protein 2 (MeCP2) is a transcriptional regulator that binds to methylated DNA. Alterations in the expression levels of this protein have been related to autism spectrum disorders. Current evidence establishes that Mecp2 is important for neuronal maturation, neurite complexity and synaptic plasticity, although the underlying mechanisms remain unknown. Previously, we have shown that Mecp2 dysfunction alters the formation and maturation of the olfactory circuit, and we hypothesized that Mecp2 plays a role in the establishment of neural connectivity. Now we aim to explore the role of this protein in axonal guidance and pruning events in the hippocampus at early postnatal stages. In the present work, we used two different mouse models of Mecp2 dysfunction to analyze the pruning of hippocampal mossy fibers. Our results show a delay in the pruning of these projections in the absence of functional Mecp2. In addition, we detected changes in the expression levels of Class 3 semaphorins, a family of guidance molecules that play an important role in the establishment of neural connectivity. Thus, the present results suggest that Mecp2 plays a role in the development/refinement of neural circuits, possibly by transcriptional regulation of guidance cues expression.

Cellular and Molecular Neurobiology
Poster Number 10 / Session I

Hippocampal NMDA receptor subunits level is modified by LTP induction

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NMDA receptors (NMDAR) are heterotetramers with 2 obligatory GluN1 subunits and 2 regulatory subunits GluN2 (A-D) or GluN3 (A-B). Hippocampal NMDARs predominantly contain GluN2A or GluN2B. During LTP induction there was a rapid replacement of GluN2B by GluN2A-containing RNMDA at the postsynaptic membrane, as was indirectly assessed by electrophysiology (Bellone and Nicoll, 2007). In this work we evaluated each major subunit by western-blot at 0', 30' and 70', after LTP induction (in fresh rat hippocampal slices) by theta burst stimulation (TBS). At 70' after LTP induction there was a significant increase in GluN1 and GluN2A but not in GluN2B level. To determine if there was de novo synthesis of the subunits, hippocampal slices were perfused either with actinomycin D (ActD) or cycloheximide (CHX) and then stimulated by TBS. CHX inhibited LTP induction. There was neither increase in GluN1 nor in GluN2A levels. ActD did not prevent LTP induction/establishment. In these slices GluN2A, though not GluN1, increased to similar levels to those reached with LTP without any drug treatment. Therefore, the GluN1 increase involves transcription and translation, while the GluN2A increase mainly depends on translation. Both, GluN1 and GluN2A increase, seems to be mainly due to translation of preexisting mRNAs, while transcription would be required for later stages in plasticity, opening the possibility that changes here reported modify NMDAR function.

Cellular and Molecular Neurobiology
Poster Number 11 / Session II

Wnt-CAMKII signalling pathway is involved in the neurotoxicity of glyphosate in cultured neurons.

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Glyphosate (Round Up) is the most common herbicide used around the world. Very few evidences have been reported about its toxicity on the nervous system in mammals. We evaluated its potential effect through in vivo and in vitro assays. We found that animals exposed to glyphosate during gestation period showed a defect on their reflex responses and the motor activity. In order to identify the mechanism of this neurotoxicity we perform assays using cultured neurons. We found that hippocampal neurons exposed to glyphosate elicit a delay on the development characterised by a decrease in axonal elongation and neuronal complexity. Wnt proteins play a critical role during nervous system development. They function as key modulators for the formation of neuronal circuits and functioning. Particularly, Wnt5a is involved in axonal growth and guidance. We observed that the expression of Wnt5a is decreased in neurons exposed to glyphosate during differentiation. To go further, we evaluated the Wnt signalling pathway involved in the glyphosate neurotoxicity. We found that glyphosate treatment lead to a decrease in the level of phospho-CAMKII in cultured neurons. Importantly, this effect was reverted when Wnt5a was added to the medium and these neurons showed a morphology similar to controls.

Cellular and Molecular Neurobiology
Poster Number 12 / Session III

Role of neurotrophins on astrogliosis induced by mechanical injury

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Neurotrophins have been extensively studied for their ability to support neuronal survival via Trk receptors, and to induce apoptosis via the p75NTR. However, the p75NTR is also detected on cell populations that do not undergo apoptosis in response to neurotrophins, such as astrocytes. In particular, p75NTR expression is induced on astrocytes during development and after seizure-induced injury. P75NTR receptor also mediates the anti-proliferative effect of the neurotrophic growth factor (NGF) on hippocampal astrocytes. In this study we investigated whether neurotrophins and their receptors influence different aspects of the astrogliosis induced by a mechanical injury. In vivo we showed that, after a stab injury, p75NTR increased in the tissue surrounding the injured area while TrkB-t decreased, although the specific role mediated by these receptors after a lesion remains unclear. In our in vitro experiments we observed that a scratch lesion increased levels of p75 NTR in astrocytes and NGF increased the migration of astrocytes after the lesion. These results are consistent with the idea that activation of p75NTR may serve to modulate gliosis after injury.

Cellular and Molecular Neurobiology
Poster Number 13 / Session I

An in vitro model of SE induces neuronal death and changes in the levels of TrkB, pTrkB and p75ntr receptors in a mixed culture of neurons and astrocytes

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Previous studies from our laboratory showed that an in vitro model of status epilepticus (SE) (3 hours of deprivation of Mg+2) induces an increase in intracellular calcium, neuronal death and mobilizes TrkB and p75 receptors to the plasma membrane. In recent experiments using hippocampal neuron cultures, it has been observed that SE in vitro increases the levels of nitric oxide (ON) and induces a marked increase in levels of tubulin tyrosinated immediately after excitotoxic stimulation. In another series of experiments, it was characterized and evaluated the effect of the presence of astrocytes on neuronal death and on the levels of TrkB, pTrkB and p75ntr receptors after 3 hours of SE in vitro. It was observed, using immunocytochemical techniques, that there is a significant decrease in the number of nuclei, determined by DAPI and NeuN, 18 hours after the excitotoxic event. It was determined by Western Blot that SE in vitro induces a decrease in the levels of TrkB, pTrkB and p75ntr immediately after the excitotoxic event. It was observed that the levels of p75ntr receptor were recovered after 6 hours. Future experiments will be necessary to determine the role of these events and of astrocytes in the neuronal death observed in this model of SE in vitro.

Cellular and Molecular Neurobiology
Poster Number 14 / Session Il

Reprogramming circuit connectivity in postmitotic cortical neurons

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Much of the richness and diversity of our perceptions and actions is rooted in the neuronal circuits of the neocortex. The assembly of these highly specialized circuits during development relies on the precisely coordinated generation, migration, and differentiation of hundreds of distinct neuronal subtypes. While the genetic programs acting in cortical progenitors to control the generation of these neurons are increasingly understood, whether these programs are active and can be manipulated in postmitotic neurons to alter subtype identity and circuit connectivity is unknown. Here, using a new in vivo gene delivery method to rapidly manipulate gene expression specifically in postmitotic neurons, we investigate the molecular controls over neuron-type specific circuit assembly in the neocortex. By manipulating gene expression in layer IV thalamorecipient neurons of the postnatal somatosensory cortex, we can reprogram their molecular identity, physiology, and input/cortical connectivity, even several days after their birth. These results reveal a largely unsuspected level of functional plasticity in postmitotic neocortical neurons, and provide a powerful tool to genetically re-engineer neural circuits in vivo to investigate their developmental assembly and function.

Cellular and Molecular Neurobiology
Poster Number 15 / Session III

Transcriptional Regulation of Late Neurogenic Events in the Neural Tube

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This work focuses in understanding the genetic mechanisms that control the differentiation of neuronal cell types in the embryonic spinal cord. We are interested in a recently described population of spinal neurons, the CerebroSpinal Fluid contacting Neurons (CSF-cN), that originate in the ventral neural tube late during embryonic development. Genetic lineage tracing in vivo experiments and expression analysis in mice show that CSF-cN progenitors express both the transcription factors Ascl1 and Gata3. We show that Ascl1 is required for CSF-cN differentiation, as they are missing in Ascl1 KO mice. We temporally restricted Ascl1 expression using conditional KO mice, revealing that Ascl1 exerts its critical actions around the time of CSF-cN differentiation. Our results indicate that Gata3 plays a key role in CSF-cN development, as these neurons are severely affected in the absence of Gata3. We determined that Ascl1 precedes Gata3 expression and that Gata3 is absent in ventral progenitors from Ascl1 mutants. On the contrary, no change was found in Ascl1 expression in Gata3 absense. In summary, we identified two key and specific regulators of CSF-cN specification. Our results show that Ascl1 and Gata3 act sequentially in controlling late neurogenic events in the ventral neural tube.

Cellular and Molecular Neurobiology
Poster Number 16 / Session I

A NOVEL VISUAL CYCLE IN THE INNER RETINA OF CHICKEN

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We previously reported light responses in GUCY1* (blind) birds mediated by the inner retina and the presence of intrinsically photosensitive retinal ganglion cells expressing the photopigment melanopsin in the retina of wt chickens. Bistable photopigments responsible for photosensitivity may use a different visual cycle in the inner retina for chromophore regeneration that relies upon distinct isomerase activities. In the present study, we investigated the expression and activity of different visual cycle enzymes and levels of retinal chromophores (11-cis RAL and all-trans RAL) in the inner retina of wt birds. Levels of 11-cis RAL were higher in the ganglion cell (GCL) and inner nuclear (INL) layers from light-adapted birds as compared with those in the dark with higher levels of all-trans RAL in this condition. Also, the photoisomerase RGR was expressed in the GCL which colocalized with Muller cell markers whereas different retinol deshydrogenases were seen in the retina and Muller cell cultures. Isomerase activity was only found in the INL while acyl CoA:retinol acyltransferase (ARAT) was observed in both INL and GCL. These results suggest that a novel visual cycle takes place in the chicken inner retina to support retinoid isomerization in non-visual photosensitive cells.

Cellular and Molecular Neurobiology
Poster Number 17 / Session II

Towards a two-hit model for TDP-43 proteinopathies: effects of hypoxia in transgenic TDP-43 mice

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Recent studies demonstrated that TDP-43 is a major disease protein in a group of neurodegenerative disorders now collectively referred to as TDP-43 proteinopathies. In these conditions, TDP-43 is redistributed from its normal nuclear localization to form cytoplasmic insoluble aggregates. In an effort to understand the pathophysiology of these diseases, we previously developed transgenic mice with inducible neuronal expression of a cytoplasmic TDP- 43 species. It was recently proposed that nuclear import defects are only one of the key steps that are involved in the pathological cascade, and that development of full-blown pathology requires a second (or multiple) hit(s). We are currently analyzing if acute exposition to hypoxia potentiates the neurodegeneration, gliosis and aggregate formation observed in our transgenic TDP-43 mouse model. We found that 72 hs after a 90 min exposure to 7% O2, transgenic mice display increased astrogliosis in specific brain areas (cortex and dentate gyrus) respect to normoxic TDP-43 mice, as demonstrated by double immunofluorescence with GFAP and hTDP-43 antibodies. We expect to identify early neurotoxic processes, and to determine if TDP-43-related neurodegenerative cascades are functionally linked to a pathological response to hypoxia.

Cellular and Molecular Neurobiology
Poster Number 18 / Session III

Characterization of Neural Stem Cells in the Olfactory Epithelium: Role of Sox2 and Wnt/B-catenin signaling pathway in neural differentiation.

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The vertebrate olfactory epithelium (OE) has been known for its remarkable characteristics of actively generating olfactory receptor neurons throughout adulthood, and rapid neuronal regeneration after extensive damage to the tissue. Identity and characteristics of Neural Stem Cells (NSC) in the OE are still unknown. Previous studies found that Wnt signaling, acting through Fz5 receptor is necessary for Sox2 expression, which in turn promotes neural differentiation in the Xenopus laevis retina. In the present study, we analyze the expression of NSC markers in the X. laevis OE by immunofluorescence. Moreover, we described a significant increase in the number of proliferative basal cells, and the number of cells expressing Sox2, during regeneration after the extensive damage of the OE by the treatment with ZnSO4. Analysis by RT-qPCR showed a trend to increase Sox2 expression in the OE during regeneration, however increase was not significant. Furthermore, activation of Wnt/β-catenin signaling pathway increases in basal cells of the OE during regeneration. Nevertheless, most proliferating cells are not activating the Wnt/β-catenin pathway or expressing Sox2, suggesting a possible role in the maintenance of multipotentiality instead a role in the proliferation of NSC in the OE.

Cellular and Molecular Neurobiology
Poster Number 19 / Session I

Tyrosine residue 251 is critical for M6a-induced neuroplasticity

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Neuronal glycoprotein M6a is involved in neuronal plasticity through unknown mechanisms. Recently a phosphorylated form at tyrosine(Y)251 has been found in the C-terminal region of M6a in mouse brain. Signaling phosphorylated proteins on tyrosine residues are specifically recognized by Src Homology 2 (SH2) modular protein interaction domains. Moreover, an in silico analysis showed that it could be a target of Src family of kinases. Therefore, the aim of this work is to establish how the phosphorylation state of Y251 is involved in neurite outgrowth and filopodia formation. To this end, we expressed Y251A-M6a (non-phosphorylatable) and Y251D-M6a (constitutively phosphorylated) in rat hippocampal neurons and cell lines and we quantified neurite outgrowth and filopodia formation. The results showed that in both primary culture of neurons and N2a cells the Y251A mutant failed to promote the formation and extension of neurites. In contrast, there are no significant differences in filopodia density in both neurons and Cos-7 cells, where all constructs showed the same ability to promote filopodium formation. Taken together, these results suggest that the Y251 residue of M6a contributes to the regulation of neurite outgrowth but not to filopodia formation. Although, this effect could be achieved by the interaction of Y251 residue with the SH2 domain of the Src kinases, further studies will be needed to prove this hypothesis.

Cellular and Molecular Neurobiology
Poster Number 20 / Session II

Does ENA regulate SRF activity? a possible mechanism to explain the cell death induced by ENA downregulation

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Neuronal polarity is essential for input–output processing and appropriate flow of information in neuronal networks, contributing to the correct function of the nervous system. The complex and polarized morphology of neurons is maintained and dynamically modified by microtubules and the actin cytoskeleton. Among actin regulatory proteins, ENA/VASP is a conserved family which is critical for both filopodia formation and elongation. We have previously demonstrated that ENA/VASP downregulation in mouse hippocampal neurons generate axonal retraction, which subsequently induces neuronal death through an apoptotic mechanism. To further characterize the mechanism of neuronal death triggered by ena in vivo we now investigate its interaction with blistered (bs), the fly ortholog of SRF. SRF is a transcription factor regulated by actin levels and plays an important role in proliferation and survival. We hypothesized that changes in the dynamics of the actin cytoskeleton, produced by ena silencing, modulates the activity of the transcriptional cofactor MRTF, which regulates the activity of BS. To study this hypothesis we are performing behavioral and molecular assays through deregulation of bs expression in the context of reduced ena. These results will shed light on how reduced ENA levels induce neuronal death.

Cellular and Molecular Neurobiology
Poster Number 21 / Session III

Development of viral vectors to express exogenous β-amyloid precursor protein (APP) in cell cultures

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B-Amyloid (BA), a peptide generated by the metabolism of B-Amyloid Precursor Protein (APP), is involved in neurotoxicity in Alzheimer's Disease (AD). Understanding APP and its relationship with AB-induced neurotoxicity is critical to the study of AD. This study was proposed to set parameters in the use of lentiviruses as a tool for expression of exogenous APP in neurons and in other cell types. Two kind of lentivirus were generated in the laboratory: One containing Yellow Fluorescent Protein sequence as a reporter, which was used to set parameters for the generation of infenctive viral particles, and the other was intended to express exogenous APP. Both type of viruses were positively used to infect HEK293T, CHO cells, astrocytes and neurons from rat hippocampus. The infection efficiency was calculated by epifluorescence microscopy. The infection percentage was proportional to volume of virus used to infect HEK293T and CHO cells but not to infect neurons. Although glial cells were infected, virus showed a greater preference for neurons than glia. We could express exogenous APP in HEK293T cells and in mixed cultures of neurons and astrocytes from rat hippocampus. Exogenous APP of infected CHO cells could not be visualized by Western blot. This technique has proven to be effective in vitro, and will be adjusted for studies in vivo.

Cellular and Molecular Neurobiology

Poster Number 22 / Session I

THE KINESIN PROTEIN KIF17 EXPRESSION IS INCREASED IN AN EXPERIMENTAL EPILEPSY MODEL

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KIF17 is a neuron specific motor protein acting in the somatodendritic region of neurons and transports different components to specific destination in a microtubule and ATP dependent manner. KIF17 transports vesicles containing NMDA receptors from the cell body to the postsynaptic sites. We have previously observed an alteration in the expression of NMDAR subunits NR2A, NR2B and PSD-95 (which binds to NMDAR subunit) after the administration of the convulsant drug 3-mercaptopropionic (MP). The objective of this work is to study the effect of repetitive administration of the convulsant drug MP on KIF17 expression in hippocampus and cerebral cortex. Wistar rats (250-300g) were daily injected with MP (45mg/kg), or saline (control) during 4 days. One day after the last injection, brains were processed for immunoassays, using antiKIF17 as primary antibody. Results: Immunohistochemical studies showed KIF17 expression in different hippocampal areas and cerebral cortex. After the administration of MP an intense immunoreactivity was observed in pyramidal and granular cells of the hippocampus and in the different layers of the cerebral cortex. It was observed an increase of 200-290% with respect to control in CA1, CA2-3, Hillus, Dentate Girus (DG) and Subiculum, while in cerebral cortex a rise of 170% was determined. These results show a great enhace of hipocampal and cortical KIF17 expression suggesting a participation of this motor protein in MP-induced hiperactivity

Cellular and Molecular Neurobiology
Poster Number 23 / Session II

The SNAREs SNAP23, VAMP4 and syntaxin6 are necessary for the establishment of neuronal polarity

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Two different types of regulated exocytosis have been described in both neurons and non neuronal cells: i) Regulated secretory exocytosis to release specific products that are segregated in the organelle lumen (e.g. neurotransmiters) and ii) Regulated exocytosis for non secretory purposes . Results from our laboratory demonstrated that the latter phenomenon is involved in the regulation of plasmalemmal precursor vesicles (PPVs) exocytosis during initial axonal outgrowth and is essential for the establishment of neuronal polarity. This process requires activation of the small GTPase TC10 and the exocyst complex by the IGF-1 receptor pathway. We have extensive knowledge about the regulatory components involved in synaptic vesicle exocytosis but little is known about the regulation of PPVs fusion with the plasmalemma. The experiments shown here were designed to identify the SNAREs involved in PPVs fusion and the establishment of neuronal polarity. Our results showed that SNAP23, VAMP4 and syntaxin6 are expressed early in differentiating neurons and exhibit a polarized distribution at the young axon. Loss of function experiments demonstrated that the expression of these three proteins is necessary for the establishment of neuronal polarity. We are now conducting experiments to obtain direct evidence about the role of SNAP23, VAMP4 and syntaxin6 in the regulation of PPVs fusion in differentiating neurons.

Cellular and Molecular Neurobiology
Poster Number 24 / Session III

Analyzing the role of Wnt pathway proteins at the vertebrate neuromuscular junction through in vivo electroporation.

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Wnt pathways regulate several features of synaptic assembly. The neuromuscular junction (NMJ) is an archetypal model to study synapse formation, growth and maturation. In cultured muscle cells, Wnt3 induces early events of postsynaptic differentiation whereas overexpression of the Frizzled-9 (Fz9) receptor decreases postsynaptic assembly. Here, we have setup in vivo electroporation to address the role of Wnt ligands and their receptors at the vertebrate NMJ. To this aim, we have designed vectors to express equivalent amounts of mCherry along with HA-tagged forms of relevant genes. These plasmids also allow the stable integration of cDNAs into the host chromosomes. Optimal conditions were standardized to combine the electroporation of chick embryo spinal cords, or post-natal mice muscles, with immunohistochemical labeling. We have achieved efficient expression of fluorescently trackeable cDNAs in chick spinal cord and mouse skeletal muscles. In developing motor neurons, Wnt3HA becomes distributed in a punctate pattern along the axonal projections and the distal growth cone tip, suggesting anterograde secretion and trophic function. In turn, overexpression of Fz9 in post-natal muscles inhibited the clustering of postsynaptic proteins, whereas its inhibition enhanced it. Our in vivo approach represents a powerful tool to analyze the contribution of Wnt pathways to different features related to the assembly of the vertebrate NMJ. (Funded by FONDECYT 1100326 and CMA Bio-Bio).

Cellular and Molecular Neurobiology
Poster Number 25 / Session II

Presynaptic calcium channels regulation by the ghrelin receptor, growth hormone secretagogue receptor type 1a (GHSR1a) activity

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Understanding the neural mechanisms underlying appetite control has became crucial for public health due to the world obesity pandemic. Ghrelin is the only peptide hormone known to increase food intake. Thus, a comprehensive understanding of ghrelin neurophysiological effects is necessary to design safe ghrelin-based clinical treatments. Ghrelin acts via GHSR1a, a G protein coupled receptor that has unusual high basal activity. In neurons, GHSR1a regulates gene expression, electric activity and neurosecretion. Here we tested if basal and evoked activity of GHSR1a modifies presynaptic calcium channels activity as a mechanism to control neurotransmitter release. For this, we performed cell-attached patch-clamp recordings in HEK293 cells expressing GHSR1a and CaV2.2 channels. We found that the amount of GHSR cDNA plasmid used during the transfection inversely correlates with the CaV2.2 basal current level. Of note, CaV2.2 basal currents level is not affected by the co-expression of a mutated form of GHSR1a that lacks constitutive activity. On the other hand, ghrelin-stimulation inhibits CaV2.2 basal current levels in a concentration-dependent manner. We then conclude that basal and evoked GHSR1a activity inhibits presynaptic calcium channels and this effect could count for the physiological effect of ghrelin at presynaptic terminals. We are currently investigating the pathways mediating this effect and the effect of newly synthesized agonists and antagonists of GHSR1a.

Cellular and Molecular Neurobiology
Poster Number 26/ Session III

Deconstructing the cell-specific transcriptional code of the dopamine D2 receptor gene

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The dopamine D2 receptor (D2R) controls pituitary prolactin secretion and plays a major role in the central control of locomotor activity and cognitive functions. Despite the significance of dopamine in normal physiology and in serious conditions of high prevalence like Parkinson disease and drug abuse, the molecular mechanisms that control the expression of D2R gene (Drd2) in different tissues remain unknown. It was shown that transgenic mice carrying a BAC (BX37) containing EGFP inserted in Drd2 exon 2 express the reporter protein in most brain areas where this receptor is normally found. In order to study the regulatory regions controlling Drd2 expression we constructed various transgenes that express the red fluorescent protein Tdimer2 driven by different fragments of the Drd2 gene. Here, we show that transgenic mice harboring a 5 kb fragment upstream of Drd2 exon 1 express Tdimer2 only in the the intermediate lobe of the pituitary. The additional presence of a 10 kb intronic region downstream of Drd2 exon 1 (transgene -5/+10_Drd2Td2) showed Tdimer2 expression in lateral septum and midbrain neurons. Compound transgenic mice expressing BAC BX37 and -5/+10_Drd2Td2 showed coexpression of both fluorescent markers indicating that the 10 kb intronic region proximal to exon 1 is likely to contain a specific enhancer for midbrain DA neurons. Additional pedigrees under analysis will be also presented.

Cellular and Molecular Neurobiology
Poster Number 27 / Session I

Translational regulation at the synapses: dynamics of mRNA silencing foci upon synaptic stimuli.

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A large number of mRNAs encoding several functions are shipped as silenced synapses by way of large ribonucleic particles known collectively as \"mRNA transport granules\". Synaptic activity regulates the translation of localized mRNA. Upon returning to the resting state, the basal levels of translation are recovered. It is unknown how degradation of mRNAs and the uptake of mRNAs into granules or mRNA silencing foci help to regulate local protein synthesis at the synapse. All these processes are mediated by RNA binding proteins, which have not been identified in all cases. We identified a novel structure, functioning as translational repressors in neurons and form silencing foci, which we called NPSAXs. That structure is forming foci in dendrites and synapses, and does not contain some RBPs components, and is distinct from processing bodies and stress granules. The NPSAX adjacent to post-synapses are disassembled upon mGlutR stimulation whereas NMDAR activation reinforces their aggregation. These results suggest that XRN1 act as translational regulators in post-synapses regulating the expression of transcripts involved in synaptic plasticity.

Cellular and Molecular Neurobiology
Poster Number 28 / Session II

Light modifies Sonic hedgehog protein profile

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In vertebrates, the primary cilium is a microtubule-based organelle that extends from the cell surface as a single, non-motile structure, and is present on most cell types in embryonic and adult tissues. Photoreceptors are the unique cellular type in the retina that possesses a primary cilium which is involved in the maintenance of the outer segment (OS) of cones and rods. The morphogen sonic hedgehog (Shh) is essential for photoreceptor differentiation and retinal cell survival through development. In addition, Shh is expressed in the retina during postnatal growth but its function is unclear. It is well known that Shh pathway take place in the non-motile cilium. In this work we studied the Shh protein response and acetylated tubulin that labels the cilium, in a model of visual hypostimulation, by immunohistochemistry and western blot analyses. We found differences both in Shh and tubulin proteins that indicate an epigenetic modulation of the OS by light. These results support our previous hypothesis that light modifies Shh protein profile, which in turn possibly could modify the cilium and therefore the outer segment. UBACYT 20020090200198

Cellular and Molecular Neurobiology
Poster Number 29 / Session III

ALPHA- SYNUCLEIN AFFECTS RESPIRATORY CHAIN AND ITS INTERNALISATION COULD INVOLVE THE TRANSPORTER OF OUTER MEMBRANE

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Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the Substantia Nigra of the midbrain. Alpha-Synuclein (AS) is a 15 KDa protein expressed in the central nervous system and is the major component of the protein aggregates in PD. It was proposed that in early steps of AS aggregation, toxic oligomeric species are formed that may lead to mitochondrial dysfunction, fragmentation and apoptosis. The aim of this work is to characterize the interaction of AS with the membranes of intact mitochondria and the effects of the incubation with AS on mitocondrial function. The status of the respiratory chain was analyzed in a high resolution oxygraph after incubation of rat brain mitochondria with AS (0, 1, 10 and 100 µM). A defect in global respiration was observed at 100 µM. In addition, the activities of the individual respiratory chain complexes were measured. Mitochondria were isolated from SH-SY5Y cells and incubated with fluorescent labeled AS (0, 1, 10 µM). In previous studies we showed that AS interacts with the mitochondrial outer membrane and that is internalised upon exposure ot 10 µM AS. Sensitized emission FRET revealed efficient transfer between AS and the outer membrane TOM20 transporter, suggesting an interaction between these proteins. The combined results suggest a direct effect of AS on the energy metabolism of mitochondria with a possible relevance to cytopathology in PD.

Cellular and Molecular Neurobiology

Poster Number 30/ Session I

Brefeldin A ribosilation substrate (BARS) is involved in neuronal differentiation and neocortex development

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BARS have been reported to control vesicular transport from the Golgi Apparatus (GA) to the somato-dendritic plasma membrane. By means of in utero electroporation (IUE) of a short hairpin (sh) RNA to suppress endogenous expression of BARS we have explored its role during brain formation.The results obtained show that 2 days after GFP IUE 85% of the neurons acquired a bipolar morphology and started to migrate along the cortical plate (CP). At the same time point only 39% of the cells expressing shBars-GFP exhibited the typical bipolar form while 61% of them displayed a multipolar morphology. When examined 4 days after IUE control GFP expressing neurons have reached superficial layers of the CP whereas the shBars-GFP counterparts remained in deeper positions. We also examined the position of the GA 2 days after co-IUE with GalT2 and found that in 75% of GFP+ neurons the GA localized at the base of the leading process that guides migration along the CP. By contrast almost 50% of shBars-GFP co-expressing neurons localized this organelle at the opposite pole. Together, these observations suggest a role for BARS in neuronal differentiation as well as cortical lamination. This might be due to its role in controlling Golgi-derived membrane trafficking. Supported by CONICET and ANPCyT.

Cellular and Molecular Neurobiology
Poster Number 31 / Session II

GABAA RECEPTOR ACTIVATION ARE INVOLVED IN DIFFERENTIATION OF EMBRYONIC HYPOTHALAMIC NEURONS DEPENDING OF SEX

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GABA is the main inhibitory neurotransmitter in adult central nervous system; however during development it exerts trophic actions. The proposed mechanism for these effects is the activation of GABAA receptor mediated current, which elicit a depolarization and the opening of voltage-dependent calcium-channels. This calcium influx acts as a second messenger that modulates the activity of a variety of kinases. Some kinases, like CAMKII and p42/44 MAPK are involved in the GABA-induced neurite outgrowth of immature neurons. Previous results of our lab have demonstrated that hypothalamic neurons show sex differences in neurite differentiation in response to estradiol. To assess sex differences in GABA-mediated neuronal differentiation, male and female hypothalamic cultures were treated with a GABAA receptor agonist (muscimol 100μM) or antagonist (bicuculline 100μM) during 2 DIV. Neurite outgrowth, soma area, number of neurites and number of neurite ramifications were quantified by morphometric analysis in five independent cultures. Muscimol-treated cultures showed neurons with shorter axons than controls irrespective of sex ($p< 0.01$); whereas the media longitude of minor processes was larger in males than females ($p< 0.001$). The percentage of neurons in stage II is also increased in muscimol-treated male cultures (muscimol 42% vs. control 30%). The lack of immunofluorescence staining of Tau-1 protein in such neurons suggests they are arrested in differentiation.

Cellular and Molecular Neurobiology
Poster Number 32 / Session III

HIGHLY ENRICHED PRIMARY CULTURES OF CHICKEN RETINAL HORIZONTAL CELLS EXPRESS THE PHOTOPIGMENT MELANOPSIN X

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Retinal ganglion cells (RGCs) expressing the photopigment melanopsin (Opn4) display intrinsic photosensitivity. In the chicken retina, two Opn4 genes, Opn4x and Opn4m have been described of which, Opn4m was restricted to the GC layer whereas Opn4x was limited to the forming GC layer and optic nerve at early embryonic days (E), but by E15 its expression was mostly in Prox1 (+) horizontal cells (HCs) (Verra et al., 2011). The aim of this work was to purify HCs from the chicken retina to obtain primary cultures enriched in these cells. Disaggregated chicken embryonic retinas at E15 were subjected to a discontinuous 1 to 4% bovine serum albumin (BSA) gradient (Morera et al., 2012). Cells from the different phases were cultured and characterized by immunochemistry and morphology. The results show that only the fraction corresponding to 2.5% BSA contained most cells displaying PROX-1 and Islet-1 (+) immunoreactivities with a typical HC morphology resembling typical HCs. 30% of cells from the whole disaggregated retina and 80% from the 2.5% BSA gradient phase were Prox-1 (+). Strikingly, Opn4x-immunoreactivity was observed in cultures from both the 2.5 and 3 % BSA gradient phases. Cells from the 3% phase express the neuronal filament of 200 KDa (NF200) and display longer processes resembling RGCs. In conclusion, by means of this method we selectively separated specific retinal cell types and obtained primary cultures highly enriched in HCs expressing the non-visual opsin Opn4x.

Cellular and Molecular Neurobiology
Poster Number 33 / Session I

Characterization of Frizzled receptors at the vertebrate neuromuscular synapse.

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The Neuromuscular Junction (NMJ), formed between motorneurons and muscle fibers, has been used as an archetypal cholinergic synapse to study synaptogenesis in vivo. Recent evidence reveals that members of the Wnt family regulate key aspects on synaptogenesis, including the NMJ. Here, we have analyzed the localization of the Frizzled (Fz) receptors at the NMJ in vivo as well as their possible role on the clustering of acetylcholine receptors (AChRs) in vitro and in vivo, a feature of postsynaptic differentiation at the NMJ. We showed that Fz9 is localized in the membrane of skeletal muscle cells, whereas Fz4 and Fz6 co-localized with AChR in postsynaptic sites. The Fz receptors evaluated are expressed during the differentiation of the C2C12 muscle cell line. Overexpression of Fz9 decreases the area of AChR clusters, whereas its silencing with a specific shRNA plays an opposite effect. Consistently, in vivo overexpression of Fz9 inhibits AChR aggregation. Our findings suggest that Wnt pathways through Fz receptors could play key roles on NMJ synaptogenesis. These effect could be mediated by the differential expression of Fz receptors in synaptic and extrasynaptic sites of the NMJ. Funded by FONDECYT 1100326 grant to JPH.

Cellular and Molecular Neurobiology
Poster Number 34 / Session II

Polarized insertion of IGF-1 receptor and cytoskeletal dynamics in neuronal polarity

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Activation of the IGF-1 receptor (IGF1r) regulates initial axonal outgrowth; a particularly early event in neurons that have not exhibited a discernible axon (stage 2) is the segregation of activatable IGF-1r to one neurite. A second early event important for axonal specification is local microtubule (MT) stabilization in one neurite of neurons in stage 2. Are these two phenomena independent or related? Our experiments showed that: i) Application of low doses of the destabilizing drug nocodazole prevents the enrichment of activatable IGF-1r in any neurite of cells in stage 2, these neurons were not able to growth an axon; ii) Low doses of the MT stabilizing drug taxol triggers the enrichment of activatable IGF-1r in all the neurites, these neurons exhibited multiple axons; iii) In non-treated cells, the neurite exhibiting enrichment of activatable IGF-1r is the same showing increased MT stability. These results suggest that increased MT enrichment in one neurite is a prerequisite for the enrichment of activatable IGF-1r in the same neurite. Moreover, control cells or taxol treated cells were not able to grow axons in the absence of IGF-1, so that increased MT stabilization is necessary for the polarized insertion of IGF-1r but not sufficient to trigger initial axonal outgrowth.

Cellular and Molecular Neurobiology
Poster Number 35 / Session III

Myelin-Associated Glycoprotein Rescues Motoneurons From Programmed Cell Death Via RhoA Signaling Pathway.

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Myelin-associated glycoprotein (MAG) is a lectin present in the periaxonal layer of myelin that engages several axonal receptors, including Nogo-R (NgRs), which have a modulatory role on programmed cell death (PCD) of motoneurons (MNs) dependent on the activation of the neurotrophin receptor P75NTR. The small GTPase RhoA regulates diverse cellular processes such as apoptosis, through one of the effector proteins, Rho-Kinase (ROCK). The aim of this study was to analyze a possible modulatory role of MAG on PCD of MNs and elucidate the signaling pathways associated with this effect. A time course study showed that early after birth Mag-null mice have a reduction in MNs count. Also Mag-null mice exhibit increased susceptibility in an in vivo model of PCD induced by a sciatic nerve crush. Interestingly pre-treatment with a soluble form of MAG (MAG-Fc) prevented MN apoptosis in this model. Studies using an in vitro model of P75NTR-dependent PCD on spinal cord organotypic cultures and a MN cell line confirmed the modulate role of MAG. We further report the in vivo role of RhoA signaling pathway in the protective effect of MAG against MN death. Treatment with Y27632 to inhibit ROCK was sufficient to reverse the protective rol of MAG-Fc. These findings indicate that RhoA signaling pathway plays a critical rol in the protective effect of MAG against PCD of MNs during development.

Cellular and Molecular Neurobiology
Poster Number 36 / Session I

Ablation of p75NTR receptor in vivo induces an altered motor phenotype

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The Neuromuscular Junction (NMJ) is a peripheral synapse formed by motor axons and skeletal muscles. The mature NMJ is maintained partly by signaling through the neurotrophin family of growth factors. Neurotrophins signal via specific Trk high affinity receptors and the p75NTR co-receptor. Here, we have characterized the motor phenotype of a null mouse (KO) for p75NTR. The gross motor phenotype was evaluated by standard approaches at different post-natal days. Muscle fiber morphology and phenotype were studied through HE and NAHD-TR staining, respectively. NMJ maturation was assessed via morphological classification of α-bungarotoxin stained postsynaptic densities. Our results indicate that KO mice are smaller and display severe splay reflex and walking alterations compared to wild-type mice. Concomitant to a decreasing diameter of muscle fibers with age, KO muscles increase the number of oxidative slow fibers compared to controls. Remarkably, KO mice show delayed postsynaptic maturation, more but smaller postsynaptic densities, as well as increased axonal branching than controls. We believe that p75NTR-dependent signaling regulates the maturation and/or maintenance of the NMJ. As p75NTR is expressed in the three components of the NMJ, cell-type restoration of its expression will dissect its specific contribution to the motor phenotype. Funded by FONDECYT 1100326 (JPH); MINREB, P07/011-F, ICM and CARE (Conicyt PFB12/2007) (FB). VP and AG are CONICYT fellows.

Cellular and Molecular Neurobiology
Poster Number 37 / Session II

Characterization of Wnt signaling in a in vitro model of motor neuron disease

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NSC-34 cells are a well known in vitro model to study motor neuron behavior. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by motor neuron death. Mutations in the Cu/Zn superoxide dismutase-1 (SOD1) protein are associated to hereditary forms of ALS. Activation of the Wnt/beta-catenin pathway plays neuroprotective effects in models of neurodegeneration. Here, we have analyzed cellular properties and Wnt signaling activity of NSC-34 cells stably expressing wild-type (NSC-hSOD1WT) or mutated (NSC-hSOD1G93A) forms of SOD1. We found that cells seeded on poly-L-lysine plus gelatin acquire a spread and flattened appearance. NSC-hSOD1WT cells display better morphological differentiation than NSC-hSOD1G93A cells. Even though the number of cells remained similar in growing conditions, a significantly lower fraction of NSC-hSOD1G93A cells were quantified under differentiating and oxidative conditions than control NSC-hSOD1WT cells. Both NSC-hSOD1WT and NSC-hSOD1G93A cells accumulated beta-catenin similarly. However, NSC-hSOD1WT cells displayed higher activation of a Wnt-responsive luciferase reporter gene that NSC-hSOD1G93A cells under conditions of differentiation. NSC-hSOD1 cell lines thus represent adequate models to approach the pathophysiological mechanisms and signaling pathways underlying motor disease. Funded by FONDECYT 1100326 (JPH), 1120651 (NO), and CMA Bio-Bio

Cellular and Molecular Neurobiology
Poster Number 38 / Session III

Wnt7b through Frizzled-7 receptor regulates dendrite development by activation of CAMKII

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Wnts are glycolipoproteins that signal through different receptors as Frizzleds, RYK and ROR2 to modulate intracellular events. Binding of Wnts to their receptors activates three cascades: Wnt/β-catenin, planar cell polarity and calcium pathways. In the nervous system, Wnt proteins regulate neuronal connectivity by controlling axon pathfinding, dendrite morphogenesis and synapses. In this study, we try to identify the Wnt7b receptor and the role of CaMKII in dendritic development. Our findings suggest that Wnt7b interacts with Frizzled-7 and this interaction increases the complexity of dendrites. In addition, this effect is blocked when neurons express the CRD-Fz7 or a shRNA-Fz-7. These evidences suggest that Fz7 may act as a receptor of Wnt7b to regulate dendrite morphogenesis. To go further, we examine the Wnt-Fz signaling involved in dendritogenesis. We observe that neurons exposed to Wnt show an increase in the level of phospho-CaMKII. This effect is blocked when neurons are treated with Sfrp1, a secreted Wnt antagonist. Furthermore, treatment with KN-93, a specific CaMKII inhibitor, abolishes the effects of Wnt7b on dendrite growth. Taken together, our results indicate that Wnt7b-Fz7 signaling is critical to regulate dendritic development through the activation of CaMKII.

Cellular and Molecular Neurobiology
Poster Number 39 / Session I

Is the inflammatory process involved in bone marrow mononuclear cell migration to the injured nerve?

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We have previously described the reorganization of myelin and axonal proteins as clusters in the injured nerve. We have also proven that endogenous and transplanted bone marrow mononuclear cells (BMMC) migrate exclusively to the injured nerve. BMMC accelerate remyelination by colocalizing with Schwann cell and nerve fiber markers, promoting the disappearance of protein clusters. In the present work, our aim was to evaluate whether the inflammatory process associated with Wallerian degeneration is one of the mechanisms involved in the recruitment of BMMC to the ipsilateral nerve. To that end, we evaluated the moment when BMMC are first found in the crushed sciatic nerve through confocal microscopy. In parallel, the involvement of prostaglandins (PG) in cell recruitment was studied through the analysis of PG synthesis and BMMC migration in indomethacin-treated rats. The results obtained show that, as soon as 24 h post injury, BMMC are localized on the border of the ipsilateral nerve and, after 3 days, they are spread throughout the nerve. Immediately after the crush, the synthesis of PGD2 and PGE2 is upregulated. After 6 h, the expression of Cox-1 and Cox-2 (PG biosynthetic enzymes) is increased. Treatment with indomethacin inhibits the migration of BMMC, which suggests PG involvement in cell recruitment and migration. Further experiments are necessary to elucidate the mechanisms involved in BMMC migration and their effect in the degeneration-regeneration process.

Cellular and Molecular Neurobiology
Poster Number 40 / Session II

Research project: Revealing protective effects derived from oligodendrocyteneuron interaction via Myelin-Associated Glycoprotein (MAG)

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The present research project assesses the effect of oligodendrocyte (OL) function,focusing on their critical role as white matter extracellular glutamate modulators. Crosslinking of MAG at the cell membrane of OL by using an anti-MAG mAb (clone 513) can initiate signalling events that mimic MAG signalling via interaction with its neuronal receptors. One such event implies the promotion of OL survival by increasing the resistance to glutamate excitotoxicity. Based in previous findings and preliminary results that support this concept, our aims are: identify the mechanism of OL protection, clarify mayor components of MAG-associated intracellular signalization on OLs, characterize axonal receptors capable to stimulate this effect and analyze the effects of MAG activation on animal models with etiologies involving excitotoxic mechanisms. We propose multiple approaches in order to identify and characterize such events: oligodendrocyte-enriched primary culture, cerebellar organotypic culture, and EAE and stroke animal models. These studies can help to clarify the importance of an intact axon-myelin interaction on stability and viability of both neurons and OL. Moreover they can contribute to the development of novel neuroprotective therapies to mitigate demyelination. consequences.

Cellular and Molecular Neurobiology
Poster Number 41 / Session III

Interaction between BDNF and Opioid Peptides signaling pathways in the expression of cocaine sensitization

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Chronic cocaine exposure induces long lasting modifications in reward processing brain areas such as Pre-Frontal Cortex (PFC), Nucleus Accumbens (NAc) and Ventral Tegmental Area (VTA) that lead to cocaine sensitization. There are evidences showing that BDNF and Opioid Peptides (OP) play a critical role in the expression of cocaine sensitization and that their signaling pathways are highly modified by drug exposure. In order to elucidate if both signaling cascades interact, we evaluated BDNF, TrkB and pTrkB levels in NAc, VTA and PFC of cocaine treated mice with and without using an unspecific inhibitor of OP receptors, Naloxone. We found that chronic cocaine administration increases pTrkB levels in NAc and BDNF levels in VTA compared to control animals. These effects were reverted in naloxone pre-treated animals, remaining both BDNF and pTrkB levels similar to that observed in the control group. We conclude that both signaling pathways are closely connected and their alteration, by cocaine consumption, is one of the numerous modifications that lead to the expression of cocaine sensitization.

Chronobiology

Poster Number 42 / Session I

Circadian period is the result of the interaction between the cell autonomous clock and the BMP retrograde signaling pathway

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The circadian clock controls rhythms in behavior, physiology and metabolism. In Drosophila, and other species, some of the molecular components of the clock, as well as the neuronal network responsible to generate and sustain circadian locomotor activity have been described. To identify additional components involved in information transmision relevant for synchronization of the circadian network we carried out a genetic screen. As a result, a fly strain that shows period lengthening of daily activity rhythms was singled out. This strain alters schnurri (shn) expression, a nuclear component of the BMP signalling pathway. We showed that adult-specific activation within pacemaker cells produced a long period phenotype in locomotor behavior. Also, we found that the BMP pathway is expressed in the adult circadian system and identified some of the BMP ligands crucial for circadian coordination within this neuronal network. Interestingly, we found that the pathway is required to fine-tune circadian period in the adult brain through the regulation of clock transcription in pacemaker neurons. Thus, adult circadian period would integrate both the pace of the cell-autonomous molecular clock and information derived by other circadian clusters to ensure coherence in the circadian network.

Chronobiology

Poster Number 43 / Session II

Intrinsic GABAergic system in the Adult Rat Pineal Gland

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GABAergic markers were reported in pineal gland from different species, but their roles in the gland biology are unknown. In order to contribute in this field, we further characterized the components of the GABAergic system in the adult rat pineal gland. We also analyzed its potential relationship with the differentiation factor NeuroD1. Our hypothesis is that NeuroD1 might play an inhibitory role on the GABAergic phenotype. In this work, we characterized expression pattern of GABAergic markers and NeuroD1 protein via triple-labeling IHQ. In the pineal gland, the neurotransmitter, the biosynthetic enzymes GAD65 and GAD67, and subunits of the metabothropic receptor GABABR1 and GABABR2, are present. All these GABAergic markers were observed in a sub-population of vimentin-positive interstitial cells. We did not observe GABAergic markers in pinealocytes. Interestingly, at ZT 14, NeuroD1 localization was mainly nuclear in pinealocytes while in these interstitial cells was cytoplasmic. GABA and GABABR1 were also observed in cells present in blood vessel walls. Our results indicate that the GABAergic population in the adult rat pineal gland is represented by a small group of vimentin-positive interstitial cells and that GABAergic signaling might act on blood vessel physiology.

Chronobiology

Poster Number 44 / Session III

TIME AS A REWARD: ROLE OF DOPAMINE AND MELATONIN IN THE CIRCADIAN MODULATION OF INTERVAL TIMING

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Temporal perception is fundamental for environmental adaptation. Most organisms have developed a system to perceive time over a wide range of magnitudes, including interval timing -in the seconds-to-minutes range– and circadian timing –in the 24h range. We have previously reported that circadian disruption impaired performance of mice in a peak-interval timing task. Additionally, our results showed significant differences in time estimation along the day (Agostino et al., 2011, Brain Res. 1370:154). In this work we studied the involvement of melatonin and dopamine signaling in the interaction between circadian and interval timing. Striatal dopamine levels measured by HLPC-ED indicated a daily rhythm under light/dark (LD) conditions. This variation, however, was eliminated under constant light (LL) conditions. On the other hand, daily injections of L-DOPA improved timing performance in mice with circadian disruptions, suggesting that a daily increase of dopamine is necessary for a correct performance. Melatonin has been reported to affect dopamine signaling in nocturnal rodents. Pinealectomized (melatonin depleted) Wistar rats showed an impairment in learning ability compared to controls, indicating that melatonin could be of importance to modulate interval timing on a circadian base. Our findings add further support to the notion that circadian and interval timing share some common processes, interacting to some extent at the level of the dopaminergic system.

Chronobiology

Poster Number 45 / Session I

Flying circus: diverse effects on physiology of chronic jet-lag

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Circadian disruption from shift-work and jet-lag has been established as a health hazard in both humans and in animal models. The mechanisms by which these conditions lead to such a wide range of deleterious effects are still unclear. Internal desynchronization of physiological variables has been proposed as the potential underlying cause. We have shown that a specific chronic jet-lag schedule can alter circadian function in mice by producing forced desynchronization of locomotor activity rhythms. We have now evaluated the effects of said protocol on cancer development, metabolism and behavior. Methods. A) Mice were injected subcutaneously with B16 (melanoma) or 3LL (lung cancer) cells and then housed under control LD or conditions. Tumor latency, tumor growth and survival were compared between the groups. B) In another group of animals, weight gain and food intake was recorded under experimental and control conditions. Results. Tumor growth was significantly accelerated 6/2 by ChrA in the two cancer models studied. Animals under gained significantly more weight than under control conditions, while consuming equal amounts of food. Discussion. The forced desynchronization model we developed can be proposed as a convenient scenario to understand the mechanisms by which circadian disruption due to shift-working or jet-lag may facilitate the onset and progression of disease in humans.

Chronobiology

Poster Number 46 / Session II

Post-translational modifications of NeuroD1 in the rat pineal gland: a common element between nervous and endocrine systems.

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NeuroD1 (ND1) is a key determinant of nervous and endocrine phenotypes, such as specific cerebellar and pancreatic cells. ND1 subcellular location and its transcriptional activity are regulated by post-translational modifications. While in pancreatic β cells glucose promotes phosphorylation of ND1 and its nuclear translocation, in cerebellar granule cells neuronal activity induces a similar mechanism. In the adult rat pineal gland, we previously reported that ND1 is expressed in pinealocytes and that its subcellular trafficking is under nocturnal noradrenergic control. Based in known features of ND1 biology, we hypothesized that post-translational modifications might be regulating nuclear ND1 translocation and its transcriptional properties in pinealocytes. In this work, we evaluated ND1 phosphorylation of specific serine residues using selective antibodies via Western blot. We found that ND1 is phosphorylated on serines 274 and 336 in pineal extracts. Both phospho-serine-ND1 levels were high in nuclear fractions and low in cytoplasmic fractions from sham glands at ZT14. The opposite pattern was observed in SCGx samples. These results suggest that phosphorylation of ND1 on serine residues regulates its nuclear import in pinealocytes; this mechanism might influence ND1-dependent transcription and its potential circadian role in pineal biology.

Chronobiology

Poster Number 47 / Session III

FAST NEUROTRANSMISSION IN THE CENTRAL PACEMAKER OF THE DROSOPHILA BRAIN

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The circadian clock is a temporal filter. Based on self-sustaining transcriptional negative feedback loops, it ultimately gives rise to rhythms in physiology and behavior. In the Drosophila adult brain, the small ventral lateral neurons (sLNvs) constitute the central pacemaker. It comprises five cells, four of which rhythmically release the neuropeptide pigment dispersing factor (PDF). PDF triggers resetting signaling events in downstream targets. Aside from the PDF-containing dense core vesicles, the presence of small clear vesicles near synaptic output sites in the axonal terminals of the sLNvs suggests that additional fast neurotransmitter(s) could take part in this process. To identify this elusive fast neurotransmitter we designed a genetic screen through RNAi-mediated silencing of specific genes. Candidate genes were selected based on sequence homology with those involved in neurotransmitter pathways in unrelated species. Inducible systems were employed to define their relevance in the control of rhythmic behavior in adult flies. As a result we have identified a candidate neurotransmitter whose silencing triggers period lengthening phenotypes in an adult-specific manner.

Chronobiology

Poster Number 48 / Session I

Retrograde BMP signaling shapes a key circadian pacemaker circuit

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The neuropeptide pigment-dispersing factor (PDF) synchronizes molecular oscillations within circadian pacemakers in the Drosophila brain. It is expressed in the small and large ventral Lateral Neurons (sLNvs and lLNvs), the former being indispensable for maintaining behavioral rhythmicity under free-running conditions. How PDF circuits develop the specific connectivity traits that endow such global behavioral control remains unknown. Here we show that mature sLNv circuits require PDF signaling during early development, acting through its cognate receptor PDFR at postsynaptic targets. Yet, axonal defects by PDF knockdown are presynaptic and become apparent only after metamorphosis, highlighting a delayed response to a signal released early on. Postsynaptic expression of constitutively active bone morphogenetic protein (BMP) receptors prevents pdfr mutants miss-routing phenotype, while sLNv-restricted downregulation of BMP signaling components phenocopied pdf01. Thus, we have uncovered a novel mechanism that provides an early “tagging” of synaptic targets that will guide circuit refinement later in development.

Chronobiology

Poster Number 49 / Session II

Circadian structural remodeling of the PDF circuit adjusts synaptic contacts along the day

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Among circadian-clusters the sLNvs are considered essential. They transmit time of day information releasing PDF. We had demonstrated axonal circadian structural changes of this circuit that could imply different synaptic partners throughout day. To further understand this phenomenon we analyzed the sLNvs projections at higher time resolution and observed a less complex structure at night. Preliminary ex vivo imaging from brain cultures indicates that sLNvs changes involve fasciculation/defasciculation and active neurite sprouting/pruning. Supporting the idea that structural changes imply different synaptic targets, the number of Brp+ puncta (a marker of active zones) changes along the day, with more contacts during early morning than at night. We also found that the area covered by synaptic vesicles change in a circadian fashion. Interestingly, the structural complexity as well as Brp+ puncta are affected after adult specific electrical silencing of PDF neurons suggesting that circadian changes in membrane excitability could play a role in sustaining structural plasticity. Thus, we propose that fasciculation and neuritogenesis render different structural configurations of the sLNvs projections along the day, affecting the synaptic output of this circuit in a circadian fashion.

Chronobiology

Poster Number 50 / Session III

PIGMENT-DISPERSING FACTOR (PDF) AND CIRCADIAN ENTRAINMENT IN C. elegans (What a night Tt!)

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Circadian rhythms are driven by endogenous biological clocks and are synchronized to environmental cues. Caenorhabditis elegans is a model organism widely used in diverse areas of research but only recently adopted for chronobiological studies. Using an automated system to track nematode locomotor activity we found that C. elegans exhibits circadian rhythms with a free running period of 23.65±0.20 h that can be entrained to both light and temperature 24-h cycles. We also found that mutations in the pdf genes induced altered circadian periods (27.51±1.04 h, pdf-1 mutant under constant darkness and temperature conditions). A genetic rescue of this mutation recovers a normal circadian period (23.57±0.3 h). It is interesting that there are also differences in the number of animals that are capable of entraining to either Zeitgeber: while in wild types 47% show rhythmic behaviour in light/dark cycles, in the case of the pdf-1 mutant, only 16% do so. Other mutant strains (pdfr-1, pdf-2, pdf-1/pdf-2) provide additional evidence for the molecular basis of circadian rhythms in C. elegans. In summary, our results show that C. elegans can be entrained to the two classical Zeitgebers and that PDF, a key player of the Drosophila circadian system, plays a role in this process.

Chronobiology

Poster Number 51 / Session I

Astroglial cells through cytokine secretion modulate the circadian system

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Bidirectional interactions between immune and circadian systems have been under intensive study. We have previously reported that the peripheral inoculation of lipopolysaccharide (LPS) or the intracerebroventricular (icv) injections of interleukin (IL)-1beta or tumor necrosis factor (TNF)-alpha, cytokines strongly stimulated by LPS, delivered at CT15 (Circadian Time 12: locomotor activity onset), induce phase-delays of locomotor activity rhythm in mice. Moreover, there was no phase shifting effect of LPS in TNF receptor deficent mice. We are now assessing which are the molecular and cellular mediators of this circadian effect. We found that peripheral stimulation with low dose LPS induces the expression of cFos and Per2 in the suprachiasmatic nucleus (SCN), the circadian brain center. We have postulated that SCN astroglial cells may be an interface between the immune and circadian systems. Here we show the induction of TNF-alpha, MCP-1 and IL-6 in conditioned media from TNF-alpha-challenged SCN astrocytes, measured 2h and 24h post-treatment. Moreover, the icv delivery of this conditioned media induced phase-delays on wheel running activity rhythms. In summary, we demonstrated SCN activation by immune stimulation and a central role of proinflammatory cytokines in this circadian effect.

Chronobiology

Poster Number 52 / Session II

A cholinergic input determines the firing mode of a subset of clock neurons of Drosophila melanogaster

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The rotation of our planet generates cyclic environmental conditions to which organisms have adapted by developing an endogenous clock. This allows them to anticipate the daily changes in light and temperature to adjust their physiology and behaviors accordingly. These circadian rhythms have been extensively studied in the fruit fly where many clock genes that interlock through negative feedback loops and generate daily oscillations have been described. Clock genes are expressed in approximately 150 clock neurons in the brain, of which a particular subset, the pigment dispersing factor-expressing lateral neurons (LNvs) have been found to play a central role. Acetylcholine (ACh) has been previously described to act as an excitatory neurotransmitter on large-LNvs, however, no specific role has been suggested. Here we propose a role for ACh on determining the firing mode of large-LNvs because the addition of curare produces a shift from bursting, the more prevalent daytime firing mode, to tonic, which is normally found at nighttime. Additionally, the finding of TTX-resistant slow rhythmic depolarisations of alternating size led us to hypothesize that the large-LNvs could be not only pacemaker cells in the circadian sense but could also present endogenous rhythmic activity similar to cardiac pacemakers.

Cognition, Behavior, and Memory
Poster Number 53 / Session III

Ethanol reinforcement is mediated by the opioid system, in 5 day-old rats

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Rat neonates (5-day–old) rapidly acquire an operant response explicitly reinforced with milk (Arias et al., 2007). We evaluated ethanol reinforcing effects in pups at this age, under similar experimental conditions. Additionally, we asked about the participation mu and kappa opioid sub-systems in mediating ethanol reinforcement. Exp. 1: 5-day-old pups were trained in an instrumental response (to press with their forelimbs or head). The reinforcers were sucrose (5%) or ethanol (3%). Two subjects were simultaneously tested. One pup received the reinforcer in contingency with the operant response, (experimental pup; E). At the same time, when E performed the operant response, other pup received the reinforcer (yoked subject; Y). Pups rapidly acquired an operant response, explicitly associated with the intraoral release of ethanol or sucrose. Exp. 2: before training, pups received an injection (i.p) of CTOP (mu antagonist), nor-BNI (kappa antagonist) or vehicle. We used ethanol as reinforcer. The blockade of both receptors resulted in the absence of increases in instrumental response, when comparing with control subjects. This result is the first in demonstrating that mu and Kappa opioid sub-systems are mediating ethanol reinforcing attributes, during the first week of life.

Cognition, Behavior, and Memory
Poster Number 54 / Session I

The role of vision in auditory distance perception

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In humans, multisensory interaction is an important strategy for improving the detection of stimuli of different nature and reducing the variability of response. It is known that the presence of visual information affects the auditory perception in the horizontal plane (azimuth), but there are few researches that study the influence of vision in the auditory distance perception. In general, the data obtained from these studies are contradictory and do not completely define the way in which visual cues affect the apparent distance of a sound source. Here psychophysical experiments on auditory distance perception in humans are performed, including and excluding visual cues. The results show that the apparent distance from the source is affected by the presence of visual information and that subjects can store in their memory a representation of the environment that later improves the perception of distance.

Cognition, Behavior, and Memory
Poster Number 55 / Session II

Neurobehavioral consequences of early mother-pup separations in mother rats

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Separation of pups from the dam may evoke emotional stress in the dam. In the present study we investigated whether prolonged maternal separation (MS) is stressful for rat dams by studying parameters known to be affected by long-term stress. After delivery, female Wistar rats were subjected to either animal facility rearing conditions or daily 4,5h of MS from postpartum day (PPD) 1-21. Maternal care (pup retrieval) was evaluated at PPD 3, 6 and 9. After weaning, anxiety (elevated plus maze) and depression-like behaviors (forced swimming test) were assessed. Memory abilities (one-trial step down inhibitory avoidance) were tested either 1h or 24h after training session. Finally, c-Fos expression was examined in the amygdala. The results revealed that MS impaired pup retrieval efficiency at PPD3. Furthermore, MS increased anxiety-like behaviors and yielded high c-Fos expression in the central nucleus of the amygdala. Although there were no differences in depression-related behavior, a deleterious effect in memory retention was observed. Together this data indicates that repeated MS in the postpartum period reduce maternal care, increase anxiety and induce a reduction in the retention memory, providing further evidence for the detrimental behavioral effects of separation in dams.

Cognition, Behavior, and Memory
Poster Number 56 / Session III

Interindividual differences in Metacognition ability across many perceptual modalities

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The search for the neural basis of consciousness gave raise to several scientific theories of what consciousness is. Some theories - called HOT, for higher order theories - claim that consciousness arises when one is aware of their own mental states. In the last few years, these theories have gained support since structural and functional data has been correlated to this awareness on one's own mental states (or meta-cognitive ability). The HOT theories use meta-cognition (cognition that is about another cognitive process) as a tool for research conscious states. The individual meta-cognitive ability is empirically assessed by the correspondence between subjective reports and task performance. A key prediction of HOT theories is that individual meta-cognitive ability should be to a good extent task and modality independent, in the same manner that individual objective performance is, suggesting the existence of a common cognitive process, still to characterize. To explore the existence of this cognitive process and its variability, we conducted four behavioral experiments using different modalities, asking subjects to report meta-cognitive judgments. And also collected EEG data in several brain states searching for neural correlations of this meta-cognitive ability.

Cognition, Behavior, and Memory
Poster Number 57 / Session I

Behavioral Deficits in TDP-43-ΔNLS Transgenic Mice

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TDP-43 has recently been identified as a pathological hallmark of the neurodegenerative disorders amyotrophic lateral sclerosis and fronto-temporal lobar degeneration. We previously generated and characterized a new animal model based on the conditional overexpression in the mouse forebrain of a cytoplasmically-localized form of human TDP-43 (TDP-43-ΔNLS), and showed that these mice recapitulate key aspects of these diseases. However, the pathophysiological role of TDP-43 in behavioral responses has not been thoroughly investigated. In the present study we show that TDP-43-ΔNLS transgenic mice develop a dramatically altered rotarod performance as early as 2 weeks post-induction, a spontaneous hyperlocomotor phenotype in the open field test and a higher level of disinhibition in the elevated plus maze test. Remarkably, we found that suppression of transgene expression for 2 weeks completely reversed the motoric phenotype, including the hyperlocomotion, impaired rotarod performance and abnormal limb clasping. This conditional disease model might provide significant insights regarding the role of abnormal TDP-43 function in complex phenotypes, teasing out the effects due to altered TDP-43 levels/function and the downstream neurodegenerative processes triggered by it.

Cognition, Behavior, and Memory
Poster Number 58 / Session II

The persistence of cocaine CPP memories is modulated by dopamine in the dorsal hippocampus

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All drugs of abuse activate the mesolimbic dopaminergic system, which originates in the VTA. Recent results point dopamine from the VTA-hippocampus pathway as a key neurotransmitter in the persistence of an aversive memory when acting 12 hours after learning. The aim of this work was to evaluate if this neurobiological mechanism can be generalized to appetitive memories, specifically those related to drugs of abuse. We developed a modified conditioned place preference protocol in rats, employing cocaine, with weak and strong conditioning schedules. Next, we manipulated the persistence of those memories and tried to determine the dopaminergic mechanisms involved. To achieve this, we bilaterally infused the dorsal hippocampus with dopaminergic agonist (SKF 38393) or antagonist (SCH 23390), 12 hours after each cocaine conditioning session. Memory was evaluated at 24 hours or 7 days post-conditioning. We observed a persistent memory after SCH infusion in the weak protocol and a decreased memory after SKF infusion in the strong protocol, both results when the test was conducted after 7 days. No modifications were observed when memory was evaluated at 24 hours. Our results suggest an opposite role of dopamine in the hippocampus with regard to memory persistence, which depends on the type of memory: if it is aversive, dopamine is essential for their maintenance; if it is appetitive, dopamine might act to attenuate it.

Cognition, Behavior, and Memory
Poster Number 59 / Session III

Pharmacological dissociation of memory expression and reactivation

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It was proposed by Tulving in 1983 that memories must be reactivated first, and then a subsequent process would determine whether they can or cannot be expressed. Reconsolidation approaches open the opportunity to explore whether mechanisms mediating memory reactivation and those that underlie behavioral expression of memory can be dissociated. In the crab Chasmagnathus memory model, animals associate the training context with a visual danger stimulus passing overhead. After a strong training protocol crabs exhibit long term memory 24–96 h later. In this model, a brief exposure (5 minutes) to the training context (reminder) induces labilization and reconsolidation. We studied the effect of pre-reminder administration of glutamate receptors AMPA and NMDA antagonist, CNQX and APV respectively. We found that CNQX (1µg/g) did not impair the behavioral expression of the memory but it did impair reconsolidation. Therefore, as expected, the expressed memory became labile. In contrast, APV (1.5 µg/g) impaired behavioral expression of the memory but did not impair its ability to be reactivated. Hence, these findings suggest that NMDA receptor activation is required for memory expression but not for memory reactivation-labilization. Our findings show that when a memory is retrieved, the respective neuronal trace is reactivated although this trace may not take control over behavior.

Cognition, Behavior, and Memory
Poster Number 60 / Session I

Oleoylethanolamide attenuates cocaine-induced behaviours through a pparα receptor-independent mechanism

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Oleoylethanolamide (OEA) is an acylethanolamide that acts as an agonist of PPARα nuclear receptor to exert their biological functions, such as feeding and metabolism. Moreover, recent evidence suggests that OEA participates in the control of reward-related behaviours. However, the role of OEA-PPARα interaction in drug-mediated behaviours is still unknown. In the present work, we studied the role of OEA and PPARα on psychomotor and rewarding effects of cocaine using behavioural tests that feature core components of addiction. Results showed that an acute administration of OEA reduces spontaneous locomotion and attenuates psychomotor activation triggered by cocaine. However, PPARα receptor knockout mice showed normal sensitization to cocaine, despite the fact that OEA was able to reduce behavioural sensitization. Furthermore, CPP and reinstatement to cocaine were intact in these mice. Our results indicate that PPARα receptor has not a critical, if any, role mediating psychomotor and rewarding effects of cocaine. Thus, further research is needed to identify OEA targets that mediate its inhibitory action on cocaine-mediated responses

Cognition, Behavior, and Memory
Poster Number 61 / Session II

Hippocampal ERK1/ERK2 activation after memory reconsolidation modulation by α7 nicotinic acetylcholine

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Previously we reported that hippocampal α7 nicotinic acetylcholine receptors (nAChRs) play a critical role in reconsolidation of an inhibitory avoidance response. Extracellular signal-regulated kinases (ERK) were demonstrated to be involved in downstream signaling after α7nAchRs activation. CF-1 male mice were trained in an inhibitory avoidance task using either a mild or a strong footshock. A retention/reactivation test was given 48 hours later. Immediately after it, mice were given intra-dorsal hippocampal infusions of choline, a α7nAchRs agonist (Ch, 0.80 ug/hippocampus) or methyllycaconitine, a α7nAchRs antagonist (MLA, 10.00 ug/hippocampus). Fifteen minutes after the infusion, the hippocampi were dissected and ERK1/ERK2 activation was determined either in the nuclear and the cytosolic fractions. ERK1/ERK2 was activated differentially, depending on the training conditions (mild or strong footshock), after memory reactivation. Ch or MLA, given immediately after memory reactivation, modified ERK1/ERK2 pattern of activation. Altogether, our results suggest for the first time a molecular pathway pattern of activation (activation or inactivation) that correlates with memory reconsolidation modulation (enhancement or impairment).

Cognition, Behavior, and Memory
Poster Number 62 / Session III

PREVIOUS STRESS PREVENTS FEAR MEMORY RECONSOLIDATION AND REDUCED NR2B SUBUNIT EXPRESSION

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The retrieval of a consolidated memory results in reconsolidation, which is vulnerable to benzodiazepines interference. In a recent study we demonstrated that previous stress induced a memory trace resistant to interference after retrieval and D-cycloserine (DCS) prior to reactivation promotes retrieval-induced fragility. This suggests that stress limits the occurrence of reconsolidation. It is known that retrieval-induced lability is dependent on NR2B subunit. Therefore, the aim of the present study was to characterize the influence of stress on NR2B subunit expression after reactivation. Male Wistar rats were subjected to a stress session and later to contextual fear conditioning. Seven days later, re-exposed to the training context and sacrificed for immunohistochemistry (IHC). Our evidence show a lack of NR2B NMDA-receptor subunits enhancement expression in the amygdaloid complex and hippocampus in stressed animals, indicating that stress might be a boundary condition for the induction of reactivation-reconsolidation of contextual fear memories.

Cognition, Behavior, and Memory
Poster Number 63 / Session I

Ghrelin increases learning consolidation and facilitates synaptic plasticity through mechanisms dependent on NR2B subunits of the NMDA receptor

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Ghrelin (Ghr) is a peptide synthesized both peripherally and in the central nervous system that participates in feeding control and learning and memory. Ghr receptors are expressed in the hypothalamus and in other brain structures such as the hippocampus (Hi), a structure involved in learning and memory processes. The biochemical cascade of memory as well as Hi long term potentiation (LTP) involve the stimulation of glutamatergic receptors (AMPA and NMDA). Furthermore, a critical requirement of NMDA receptor (NMDAR) containing NR2B subunits for the induction of LTP has been demonstrated. Previously in our laboratory we demonstrated that intra-Hi Ghr administration in rats enhances memory consolidation in the step-down test (SDT) and reduces the threshold to induce LTP in Hi. However, the molecular and cellular basis of Ghr effects still remains unclear. In the present work we studied the participation of NMDAR containing NR2B subunits in the Ghr effect using a SDT and electrophysiological recordings. Our results showed that intra-Hi administration of a selective NR2B antagonist (Ro-256981) previous to Ghr partially blocked memory consolidation and increased threshold to generate Hi LTP in relation to Ghr alone suggesting that Ghr effects were partially dependent on NR2B subunit. *Equal contribution.

Cognition, Behavior, and Memory
Poster Number 64 / Session II

Switching Sides. Children use of Ostensive Cues.

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Previous studies have demonstrated that infants can recognize an adult\'s communicative intention by being sensitive to the ostensive cues (OC) used to indicate a learning context (Csibra, 2010). In contrast, infants\' ability to teach has been much less studied than their ability to learn (Strauss, 2004; Davis-Unger 2008; Battro, 2010) and therefore, we do not yet know if infants produce these OC when they want to manifest an informative intention. In the present minipaper we studied if children made use of OC - including changes in body orientation, eye-contact, eyebrow-raising and in the voice pitch - in a scenario in which they become teachers. We examined kids' use of OC in games in which a rule had to be inferred before being taught to an adult. And found, as previously reported, that children, as young as three year old, were capable of using screening-off information to learn the causal structure of biological events (Schulz, 2004). Here we show, for the first time, that children can not only detect, recognize and react to OC (Csibra, 2009) but furthermore, that they are capable of generating these signals when teaching. Our results strongly suggest that they can actively transmit knowledge to others, using well-known ostensive cues to denote a pedagogical intention.

Cognition, Behavior, and Memory
Poster Number 65 / Session III

The Emergence of Frequency Effect in Natural Reading

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While reading, our eyes gaze on the sentences making fast movements -saccades- and short fixations over the words. These fixations are not randomly distributed, their locations and durations co-vary with many parameters of the text, such as word length, class or frequency. A great amount of literature has described the relation between fixation duration and the frequency of occurrence of a word in large corpus. However, not many studies have been made concerning the emergence of this effect. In this work, we studied the evolution of fixation durations -and other parameters- as words are repeated throughout short stories. We have found that fixation duration diminishes as a repeated word is read several times in the same text, and this effect is only observed in words with low corpus frequency. On the other hand, for high frequency words fixation duration remains unchanged. Furthermore, the diminishing of gaze duration appears to vary continuously with frequency, and depends on the distance between repeated words. This kind of experiments presents reading as a dynamical process, which can incorporate new information to previous knowledge during the natural course of reading.

Cognition, Behavior, and Memory
Poster Number 66 / Session I

GABA and extinction

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Extinction memory results a challenging process to be studied because it shares a lot of features with the initial learning. However, it also involves exclusive components. As Pavlov and Konorski had remarked, the most broadly distinguished difference between initial learning and extinction learning was that initial learning certainly entailed excitatory synaptic connections, whereas extinction likely involved inhibitory synaptic connections. Considering extinction as a new memory, the modulation of GABA during its consolidation would be similar to the role described the original one. But considering the inhibitory role of the neurotransmitter and the inhibitory attributes of extinction memory, we proposed a different function for other phases of this memory, in particular during the extinction memory acquisition. Here, using an invertebrate model, we examine the role of GABA in the different extinction memory phases: acquisition, consolidation and retrieval. Finally, we advance in the characterization of GABAA receptor distribution and composition in this invertebrate model. This description will be the first step to study possible modifications in number and composition of GABAA receptor in relation with the different memory phases.

Cognition, Behavior, and Memory
Poster Number 67 / Session II

Genetic modulation of dopamine D2 autoreceptor levels in live mice

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Dopamine D2 receptors expressed in dopaminergic midbrain neurons (AutoD2R) regulate cell activity and DA release. Thus, it is likely that variations in D2 autoreceptor levels play a role in prevalent human pathologies including schizophrenia, ADHD and Tourette's syndrome. We have recently generated mice selective lacking AutoD2 and demonstrated their critical importance in regulating DA neurotransmission. To study the consequences of having reduced but intermediate levels of autoD2Rs we developed two novel genetically modified mouse models: a) an inducible knock out of autoD2Rs with temporal and dosage control, generated by crossing homozygous Drd2loxP/loxP mice with Tg (Dat-CreERT2) that express a tamoxifen inducible form of Cre in DA neurons, and b) constitutive heterozygous autoD2RKO mice obtained by mating Drd2+/flox and Dat+/IresCre knockin mice. Analysis of heterozygous autoD2R knockdown mice revealed an initial over response to novelty, appreciated as hyperlocomotion during the first two days in a 3 days habituation protocol. The inducible Cre line showed a high level of colocalization of Cre-mediated recombination within DA neurons when evaluated using a Cre reporter line. Adult mice showed hyperlocomotion immediately after receiving tamoxifen reaching a 66% increase at day 11 post injection compared to pretreatment results. Analysis of stereotyped and impulsive behaviors is under investigation and will be presented at the meeting.

Cognition, Behavior, and Memory
Poster Number 68 / Session III

Molecular and Functional Dissection of the Dopamine D2 Receptor in the Mammalian Brain

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Natural rewards and drugs of abuse exert their reinforcing properties by eliciting an anticipatory fast increase in extracellular dopamine (DA) in the dorso-ventral striatum. The dopamine D2 receptor (D2R) plays a role as a key integrator of the subjective motivational value assigned to a given reward and the preparatory and executive set of motor actions deployed to obtain it. It was reported that an allelic variant of the human D2R gene seems to be associated to a reduced number of D2R in the striatum, which in turn correlates with increased vulnerability to drug addiction and with more pleasant experiences reported by healthy non-abusing volunteers taking drugs of abuse. These observations raised the hypothesis that repetitive drug intake compensates for the decreased activation of D2Rs participating in reward circuits. To test this hypothesis we have generated a novel strain of conditional mutant mice specifically lacking D2Rs in striatal medium spiny neurons. We have verified the efficiency of the specific striatal D2R gene deletion using a transgenic reporter gene assay, in-situ hybridization and immunohistochemistry. We also showed that both, homozygous and heterozygous mutant mice are less active than wild type controls in an exploratory activity test. Ongoing studies are under development to evaluate the reaction of each genotype to the administration of cocaine and ethanol.

Cognition, Behavior, and Memory
Poster Number 69 / Session I

A behavioral phenotype detected early in development can predict the sensitivity to the stimulating effect of ethanol

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Relatively high ethanol doses (between 1.25 and 2.5 g/kg) induce acute locomotor stimulating effects in preweanling rats, an effect associated with the rewarding properties of the drug. Baseline locomotor activity predicts the magnitude of this ethanol effect in infant and adult rats. The goals of the present work were to analyze whether repeated ethanol exposure results in conditioned sensitization or tolerance of the locomotor stimulating effect, and whether a behavioral phenotype based on the initial exploration of an environment during the first postnatal week of life can predict a long-term response to ethanol. Baseline locomotor activity was registered on postnatal day 8 (PD 8). Then, subjects (PDs 8 to 12) received 0 or 2.5 g/kg ethanol before being placed in an open field containing an odor cue. On PD 15 pups were tested in an open field after being injected with ethanol (0 or 2.5 g/kg) in presence or absence of the odor. Results showed ethanol induced locomotor activating effects in infant rats (between PD8 and PD15). Repeated exposure to the drug did not induce tolerance when pups were tested in absence of the odor cue, but when the odor was present there were some evidences of conditioned tolerance to the stimulating effect. Besides, baseline level of activity (on PD 8) predicted ethanol response on PD 15, independently of the presence of the odor cue. These results suggest the possibility to use early behavioral markers to predict unconditioned effects of ethanol.

Cognition, Behavior, and Memory
Poster Number 70 / Session II

Strategy to examine molecular mechanisms required for spaced learning in Drosophila

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Increasing the amount of time spent studying improves memory retention, but the distributions of the study sessions across time is also critical. Memory that is induced by repeated training improves when training sessions are spaced over time compared to equal amount of training without spacing. This phenomenon, called the spacing effect, has been observed in humans and animal models, however, its underlying mechanisms remain poorly understood. Recent studies in a Noonan syndrome model in Drosophila demonstrated that the spacing effect depends on SHP2 tyrosine phosphatase activity levels and its effects on Ras/MAPK pathway activation. These observations have suggested that the spacing effect can be impaired in Noonan syndrome and related disorders. Since, these molecular components regulate many cellular processes involved in cellular plasticity and memory; we seek to determine whether the Egfr/Ras/MAPK pathway controls the spacing effect. Here we present some preliminary observations and a strategy to discriminate genes involved in long-term memory from those that actually can control the induction of the spacing effect. This work should expand our knowledge of the molecular processing required for spaced learning and may lead to therapeutic applications in the future.

Cognition, Behavior, and Memory
Poster Number 71 / Session III

Evaluating the role of 5-HT2a receptors in cognitive flexibility and memory interference

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Our ability to adjust our behavior to dynamic changes in the environment is called \"Cognitive flexibility\" and it is part of the repertoire of executive functions. Memory interference is the result of competing memories traces. Both mechanisms are postulated, in the literature, to depend on the activity of the Pre Frontal Cortex (PFC) since they might involve a common inhibitory control that acts over habitual responses or related memories. Clinical and pre clinical data support a role of the serotonergic system in cognitive flexibility and memory interference. Among the serotonergic receptors, the 5-HT2a has been the focus of attention since it is one of the most important post-synaptic receptors of the serotonergic system and highly expressed in cortical regions and the limbic system. One of the main problems addressing the role of 5-HT2a receptors in cognitive functions is the lack of specific drugs. Here we are using a genetically modified mouse model to study the role of the 5-HT2a receptors in cognitive flexibility and memory interference. We found that mice lacking the 5-HT2a receptor (5-HT2a -/-) show deficits in the spontaneous alternation task suggesting decrease flexibility response and low levels of discrimination in a temporal order novel object recognition task, indicating increase interference between competing memory traces. These results suggest that 5-HT2a receptors might play a role in cognitive flexibility and memory interferences processes.

Cognition, Behavior, and Memory
Poster Number 72 / Session I

Forgotten declarative memories can be reactivated

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The reconsolidation hypothesis has challenged the traditional view of fixed memories after consolidation. Recently, we demonstrated that a mild stressor, cold pressor stress (CPS), can enhance declarative memory (association between five cue-syllables and their respective response-syllables) during reconsolidation. Here, we utilize positive modulation of memory expression to determine whether 7 or 20 days old long-term unexpressed memories can be re expressed by two different memory modulators: a mild stressor or glucose, during reconsolidation. Very poor memory performance was found at reactivation (day 6 and 20 after training). CPS can enhance reconsolidation, improving the long-term expression of memory 6 but not 20 days after training. However, we found that memory performance is robust at both one and three weeks after training when a recognition test, instead free recall test was apply .Interestingly, the administration of an oral source of glucose (juice), but not a diet juice, can enhance memory during reconsolidation even 20 days after training. Consequently, the period in which this memory can be reactivated and become labile largely exceed the period in which the memory is expressed. Results are consistent with the concept that memory labilization and behavioral expression of memory are a dissociable processes.

Cognition, Behavior, and Memory

Differential brain activity during causal judgments

Poster Number 73 / Session II

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It's possible through the emission of a causal judgment by a participant, to infer the relationship perceived about two events, this relation can be modified when the circumstances change to adapt to a new set of circumstances. The experiment consisted in three phases: acquisition, extinction and test. The participants were asked to provide a judgment about the probability of the presentation of an outcome. The context changed on each phase, being X in acquisition, Y in extinction and X in test. During acquisition, the cue A always preceded the outcome and the cue B didn't. During extinction both the cue A and B were presented without being followed by the outcome. Finally, in the test phase both cues were presented but there was no feedback about the presentation of the outcome.Both, the cues and the outcomes, were geometric figures and as context different wallpapers. The task took place inside a 3 Tesla scanner using BOLD contrast to acquire the images. The task was performed by 12 participants with a range of ages between 21 and 31 years clinically healthy. A preliminary analysis of the functional images during the emission of a judgment revealed activity in cortical areas such as the occipital and prefrontal cortex and in the fusiform gyrus. This activation was more prominent during test, which suggest that during this phase there are more elements to take in to account and there is a retrospective analysis before the emission of the causal judgment.

Cognition, Behavior, and Memory

Poster Number 74 / Session III

Emotional, physiological and long-term motivational consequences of maternal ethanol intoxication during nursing

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Alcohol maternal consumption during nursing allows for early contact of the offspring with ethanol and disrupts the normal repertoire of maternal care behavior (i.e., pup retrieval and adoption of crouching behaviors). Repeated neonatal deprivation can also result in a reduced response towards rewards later in life. Objective: To analyze the emission of ultrasonic vocalization (USV) and body temperature in three-day old pups while they interact with an ethanol-intoxicated dam. Intake of natural reinforcers was assessed in these pups later in life, during infancy and adolescence. Methods: During postnatal day (PD 3), neonates interacted with dams given 0.0 or 2.0 g/kg ethanol. The pup's USV emission and body temperature was registered. At PD 16 and 30, these pups were assessed for milk or sucrose intake, while exposed or not to ethanol odor. Results: USV were higher and body temperature was lower in pups that interacted with intoxicated dams. These pups drank less milk and sucrose, but only when ethanol odor was present, during the tests conducted on PD 16 and 30, respectively. Conclusion: The interaction with an ethanol intoxicated dam induces acute emotional and physiological alterations and seems to result in the processing of ethanol orosensory cues. Re-exposure to these cues later in life significantly reduces the intake of natural reinforcers, a result suggestive of anhedonia.

Cognition, Behavior, and Memory
Poster Number 75 / Session I

Chromatic categorization in a memory task

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Several cognitive processes are based on our capacity to cluster stimuli into discrete categories. When a stimulus is identified as a member of a given category, it is no longer necessary to remember all its physical characteristics: The label that tags its membership to the category suffices to identify it and to operate with it. All subsequent computations, therefore, can be carried out with minimal computational load. There are several examples where categorical processing is evident in sensory systems, for instance in olfactory and linguistic domains. In this work we analyze the tendency to remember and process color information using chromatic categories. To that end, we develop a computer game where the player needs to hold a color in memory. Although the target colors cover the spectrum uniformly, the remembered colors cluster into categories. The clusters are evident both in an Euclidean metric defined in the space of light spectra and in the CIE xyY standard observer metric that characterizes the typical capability of trichromatic human subjects to distinguish neighboring colors. Although the exact size and position of each category depends on the subject, different players show a general trend to cluster colors around blue, green and red. Our data suggest that memory for colors is structured in terms of attractors.

Cognition, Behavior, and Memory
Poster Number 76 / Session II

Spatial learning induces increasing of argyrophilic nucleolar organizer region (AgNOR) of pallium medial neurons in toads (Rhinella arenarum)

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Spatial learning and memory related morphological changes in the argyrophilic nucleolar organizer region (AgNOR) of telencephalic neurons in the toad Rhinella arenarum were quantitatively evaluated by means of AgNOR neurohistochemical stain. The AgNORs and nuclei of nerve cells of four different telencephalic regions of toads trained in a spatial task or submitted to a similar non-contingent spatial procedure (control group) were morphometrically evaluated. Results show that relative area of AgNORs in neurons of the medial pallium (homologue to the mammalian hippocampus) increased significantly in the spatial learning group, but not in control group. This effect seems to be highly specific as it did not appear in the medial pallium area of the control group neither in septum, striatum nor amygdala of both groups. As the size of AgNORs in the nerve cell nuclei reflects the level of transcriptive activity, these morphological changes could be revealing increased protein synthesis related with learning and memory. These findings contribute to locate the subregions of the amphibian telencephalon linked to spatial learning and also indicate that the AgNOR staining technique would be a useful tool in assessing learning and memory related neuronal activity in toads.

Cognition, Behavior, and Memory
Poster Number 77 / Session III

Calcineurin as a regulator of memory formation: Mechanisms involved

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Many studies on synaptic signaling in neural plasticity support that synaptic strengthening is induced by altering the balance between protein kinases and protein phosphatases towards the side of the kinases. Conversely, synaptic depression is mediated by phosphatase activation. The phosphatase calcineurin CaN was particularly studied due to the fact that it is activated directly by Ca2+/Calmodulin signals and that it is highly present in synaptic spines. Some studies support its role as a memory constraint in consolidation in different paradigms. On the other hand, it is well known that the transcription factor NF-κB is necessary for memory formation. In the present work we studied the effect of CaN pharmacological inhibition during fear conditioning consolidation. We found that hippocampal CaN inhibition by means of the drug FK506 improved contextual fear memory. If NF-κB was also inhibited, facilitation of memory was not observed. Thus, our next studies were aimed to see if CaN acts as a negative constraint by inhibiting NF-κB signaling pathway. Preliminary results show that FK506-induced memory enhancement produced an increment in the activity of NF-κB. We discuss possible mechanisms of CaN signaling as a constraint regulator of memory formation.

Cognition, Behavior, and Memory
Poster Number 78 / Session I

Role of the mesocortical dopaminergic system in novelty-induced hyperlocomotion in a mice model of schizophrenia

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Novelty-induced hyperlocomotion is a phenotype commonly associated with positive-like symptoms in schizophrenia mice models. It mimics psychomotor agitation usually triggered by stress in an important subset of schizophrenia patients. It can be pharmacologically induced in mice by administration of either dopaminergic agonists or NMDA receptor antagonists. Early postnatal NMDAr ablation, exclusively in parvalbumin positive corticolimbic interneurons, results in histochemical and behavioral changes (including novelty-induced hyperlocomotion) compatible with a schizophrenia-like phenotype. These phenotypes emerge during young adulthood as result of an abnormal development during adolescence. With the aim of uncover the mechanisms involved in the hyperlocomotor response in this mutant we performed a series of behavioral and immunohistochemical analysis. We exposed mutant and control adult male mice to an open field in a novel or habituated environment. Analysis of immediate-early gene expression in ventral tegmental area (VTA) and medial prefrontal cortex (mPFC) showed an increased in c-Fos expression in both areas in the novelty exposed group, with a significant reduction in the number of positive cells in mPFC of mutants. We speculated that an abnormal function of mPFC could result in an imbalance in the dopaminergic system triggering the novelty-induced hyperlocomotion observed in mutants.

Cognition, Behavior, and Memory
Poster Number 79 / Session II

Quantitative Classification and Syntactic Analysis of Rat Ultrasonic Vocalizations

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Traditional studies on the ultrasonic vocalizations (USVs) produced by rats have relied on the categorization of calls by eye-inspection. This procedure is both cumbersome and prone to bias. In this work we present a method for the automatic classification of calls based on their instantaneous spectro-temporal properties. We identify two relevant properties: instantaneous frequency (F) and frequency modulation amplitude (M) and show that a USV can be segmented into discrete regions of (F,M) space. These regions correspond to: 22 kHz calls, low frequency unmodulated, high frequency unmodulated and frequency modulated. These are combined in non-random sequences defining call classes. We propose visual classification overestimates the number of classes by breaking apart continuous distributions of call properties. Finally, we explore whether rat calls are chained in stereotyped sequences supporting the existence of syntax in their vocal production.

Cognition, Behavior, and Memory
Poster Number 80 / Session III

The effect of strengthening decides the fate of a human declarative memory

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It has been demonstrated that once consolidated, a memory could be rendered labile again and susceptible to disruption or facilitation upon its reactivation. Such vulnerability diminishes with the progress of time and implies a re-stabilization phase, a process known as reconsolidation. Using a list of five pairs of non-sense syllables (a cue-syllable associated with a response-syllable), we have demonstrated that a previously consolidated declarative memory could be labilized by the presentation of a specific reminder and its re-stabilization impaired by a second training. In turn, we have previous demonstrated that repeated presentations of the proper cue-reminder strengthened the memory tested 24 h after. Here we explore a) The possibility of interfering a strengthened memory with a second task b) The strengthening effect on long term persistence and c) The possibility to strengthen an older memory. We found that a) A strengthened memory by the repeated presentations of the reminder, is less susceptible to interference. b) The strengthening effect improves the persistence of memory. Finally c) Successive reactivations of an older memory do not strengthen its trace.

Cognition, Behavior, and Memory
Poster Number 81 / Session I

Sensitivity to appetitive and aversive effects of ethanol in infant rats classified as high or low novelty-seekers.

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The association between novelty-seeking and ethanol´s motivational effects was tested in infant rats. Hypothesis: High responders will be more sensitive to ethanol's appetitive effects and less sensitive to ethanol-induced aversion. Experiments 1 and 2: Pups were classified as high or low responders as a function of locomotion in an open field. At postnatal day 14 (PD14) pups received 0.0, 0.5 1.0 or 2.0 g/kg ethanol (i.g., unconditional stimulus, US), paired with water (Conditional stimulus, CS1). At PD15, the CS1 was paired with sandpaper (CS2). In test, animals previously treated with 2.0 g/kg ethanol group avoided sandpaper and those given 0.5 g/kg exhibited preference for the CS. Exp 3: Animals were classified as high or low seekers for a novel odor (PD14). At PDs15-16 saccharin was paired with 0, 1.25 or 2.5g/kg ethanol. A decrement in saccharin intake was observed on PD 17, in animals given 2.5 g/kg ethanol. Across experiments ethanol motivational effects were not modulated by novelty-seeking. Infant were highly sensitive to ethanol-induced motivational learning, yet this response was not associated with proclivity to explore new stimuli.

Cognition, Behavior, and Memory
Poster Number 82 / Session II

Mechanisms of memory labilization

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Once a memory is consolidated, the presentation of a reminder can induce reconsolidation, involving reactivation, labilization and restabilization of the memory trace. We studied the role of the proteasome system during memory labilization in two contextual associative models, context-signal memory in the crab Chasmagnathus and fear conditioning in mouse. Our previous results show that inhibition of NF-kB during consolidation with sulfasalazine or the proteasome inhibitor MG 132, causes an amnesic effect on memory consolidation. Paradoxically, when we administered MG132 previous to the re-exposure we did not find an amnesic effect and its co-administration with sulfasalazine did not induce the expected memory impairment that normally induces the last drug. Altogether, these results support the hypothesis that the proteasome activity is necessary for memory labilization. We also studied if there is a functional role of the reconsolidation process on memory reinforcement. In both contextual associative models we re-exposed the animals several times either on the same day or in consecutive days. Memory reconsolidation was reinforced when crabs were re-exposed three times on the same day while no reinforcement was found when they were re-exposed over several days. Mice showed no reinforcement in any of the tested conditions. The implication of these results is discussed in the context of previous findings in inhibitory avoidance in rats and episodic memory in humans.

Cognition, Behavior, and Memory

Poster Number 83 / Session III

Mild and severe perinatal asphyxia induce opposite effects on cocaine sensitization in adult rats

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Dysregulation of dopaminergic transmission is one of the long-lasting consequences of perinatal asphyxia (PA). Since the dopaminergic system plays a major role in addiction processes, we hypothesized that PA could be associated with an increased vulnerability to psychostimulant addiction. Adult rats born vaginally (CTL), by caesarean section (C+), or by caesarean section followed by 15 min (PA15) or 19 min (PA19) of birth asphyxia were submitted to a cocaine-induced behavioral sensitization test and the expression of tyrosine hydroxylase (TH) in the dorsal striatum was measured. During 5 days, all groups increased their locomotor activity in response to daily cocaine (coc) injections (15 mg/kg). 7 days later, CTL and C+ displayed a robust locomotor sensitization to an acute priming dose of coc (7.5 mg/kg). However, the acute priming injection of coc elicited an attenuated sensitized response in PA19, while PA15 displayed an exacerbated sensitized response. Expression of TH was significantly higher in PA15 compared to all other groups. These results demonstrate that PA induces opposite effects on behavioral sensitization to coc depending on its severity, and suggest that the increased TH levels in PA15 could be associated with the displayed hypersensitized response.

Cognition, Behavior, and Memory
Poster Number 84 / Session I

Molecular mechanisms involved in the effect of IL-1β on consolidation of fear memory

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Pro-inflammatory cytokines such as IL-1β may affect cognitive processes by impairing synaptic plasticity through activation of MAP kinases and by inhibiting downstream mediators. IL-1β significantly influences consolidation of memories that depend on hippocampus. However, the mechanisms by which this inhibition occurred are not clearly established yet. We previously reported that IL-1β can induce a decrease in glutamate release during consolidation of contextual fear memory. Preliminary results showed that intrahippocampal administration of IL-1β increased p38 phosphorylation and that the treatment with SB203580, an inhibitor of p38 phosphorylation, could reverse the effect of the cytokine on glutamate release. IL-1β administration also reduced ERK2 phosphorylation, a MAPK critically involved in memory consolidation. Here, we showed that the treatment with D-cycloserine, a partial agonist of the NMDA receptor, reversed the effect of IL-1β on ERK2 phosphorylation. The evidence presented is consistent with the idea that the impairment induced by IL-1β on memory consolidation could be mediated through the activation of p38 MAPK and consequently the decrease in glutamate release.

Cognition, Behavior, and Memory
Poster Number 85 / Session II

Conscious Access and Attentional Blink during Eye Movements

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When we look at a visual scene, we spontaneously move our eyes producing a set of fixations, separated by ballistic eye-movements or saccades. This work was aimed to study the temporal dynamics of conscious access during eye-movements. To address this issue, we designed a set of gaze-contingent experiments where the fixation duration was under subjects\' control, but constrained to a distribution similar to fixations in natural tasks. We show that conscious access is restricted to a temporal window embedded in the fixations. However, while subjects' visibility is close to perfect during that window, introspective confidence increases with a slower rate. This asymmetry can be regarded as an accumulation of evidence that biases the selection of information, becoming more likely to select items flashed close to the outgoing saccade. When presented a rapid succession of visual stimuli, participants often fail to detect a second salient target, a phenomenon referred as the attentional blink. We show that the blink vanishes when both targets are presented within a fixation (far from the saccadic boundaries) and that it recovers more rapidly in successive fixations. These results support current views that the blink results from a discrete structuring of attention and provide evidence that eye-movements play an important role in the formation of those episodes.

Cognition, Behavior, and Memory
Poster Number 86 / Session III

Hippocampal muscarinic acetyolcholine receptors modulate memory reconsolidation of an inhibitory avoidance task in mice

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CF-1 male mice were trained in an inhibitory avoidance task using either a mild or a high footshock. A retention test was given 48 hours later. Immediately after it, mice were given intra-dorsal hippocampus infusions of either oxotremorine (OXO, a muscarinic acetylcholine receptor agonist, 1.00-10.00 ng/hippocampus), or scopolamine (SCO, a muscarinic acetylcholine receptor antagonist, 1.00-10.00 ug/hippocampus). Memory retention was tested again 24 h later. SCO impaired retention performance regardless of footshock intensit. OXO impaired retention performance only in those mice trained with a high footshock. On the contrary, OXO enhanced retention performance when mice were trained with a mild footshock. These effects were dose- and time-dependent. Retention performance was not affected in drug-treated mice that were not subjected to memory reactivation, suggesting that the performance effects cloud not be attributable to non-specific effects of the drugs. Our results suggest for the first time that hippocampal muscarinic acetylcholine receptors play a critical role in reconsolidation of an inhibitory avoidance response in mice.

Cognition, Behavior, and Memory
Poster Number 87 / Session I

Running speed modulation of neural activity in the Hippocampal-Entorhinal loop

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Hippocampus (HC) and Medial Entorhinal Cortex (MEC) are known for their prominent role in memory and spatial navigation, housing neurons with the highest spatial tuning yet reported in the mammalian brain: place cells (HC) and grid cells (MEC). It has been proposed that in order to achieve such a precise spatial firing, these circuits integrate a velocity signal through an operation called “path integration”. The actual source of this signal, however, has not been yet clarified. The main proposals are that speed is coded in a) the frequency of theta oscillations or b) the firing rate of MEC or MEC-related neurons. We present a new apparatus that allows us to control the running speed of rats while we record their neural activity. We find that the frequency of theta oscillations is unrelated to speed, but instead correlates with the strictly positive part of the acceleration. In addition, we report the finding of two new types of neuron in the MEC: putative pyramidal cells that display a conjunctive representation of speed and head direction (which we call velocity cells) and putative interneurons that respond accurately to running speed alone (which we call speed cells). Both findings combined provide evidence supporting the latter of the previously mentioned proposals, where the HC/MEC loop is thought to perform path integration over a speed signal that is coded in the firing rate of specific MEC neurons.

Cognition, Behavior, and Memory
Poster Number 88 / Session II

Defining the psychoacoustical space of vocal imitations and caricatures

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The relationship between the speaker\'s identity and the psychoacoustic parameters characterizing his/her voice has been a matter of debate in the literature and still remains elusive. Here we built a database using phrases of famous argentinian characters (targets), along with the copies produced by professional and amateur impersonators. We asked them to reproduce the original phrases before and after listening to the target phrases. We call the first type of copy a caricature (based on an internal pattern of the target that the impersonator has) and the second one an imitation (based on the actual target phrase). Our perceptual experiments showed that the identity of the speaker is better elicited by the caricatures, while voice similarity is better associated with the imitations. These results suggest that a disambiguation is needed when judging voice similarity and speaker\'s identity and reveal that, in analogy with cartoons in the visual space, acoustical caricatures exists with their own rules of formation and carrying complex identity information.

Cognition, Behavior, and Memory
Poster Number 89 / Session III

Past experience: help or hindrance to Vespula germanica foragers?

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In this study we investigated cognitive processes in Vespula germanica foragers analyzing the effects of past experience on wasp response to changing contexts. This social species frequently makes several consecutive flights between an undepleted food resource and the nest. In our experiment, carried out under natural conditions, an individual wasp collected food from a feeder located in a certain position in relation to a coloured array. After departure, food was displaced 60 cm and an empty dish was placed at the original feeding site. On its next visit, the wasp visited the empty feeder, without noticing the nearby presence of food. Our results showed that the detection of the displaced food source depended on the number of times a wasp had previously collected food from the first feeder location. Thus, four feeding experiences resulted in a significant increase in the searching time compared to one feeding experience. Why did returning foragers not detect the tangible meat, but searched over a site which no longer offered food, despite the fact that odour cues have great saliency for this species? In the present study, we discuss the delay in detection of more rewarding contexts from the perspective of the enactive theory which considers cognition as embodied action.

Cognition, Behavior, and Memory
Poster Number 90 / Session I

Altruism plasticity in children: a case study in 6-7 year olds

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Human altruism is a prosocial behavior which emerges at early stages, develops throughout life and is greatly affected by social contexts. The aim of this preliminary study was to evaluate the plasticity of altruistic behavior in 6-7 year olds, analyzing the effects of a short intervention performed in a public school in Bariloche, Argentina. The research involved 41 participants and the intervention included mindfulness practices, cooperative games and emotional security priming conducted during 10 weekly sessions. The results showed that altruism among peers significantly increased after the intervention in the experimental group, whereas in the control no change was observed. Interestingly, mindfulness practice performance improved throughout the intervention period. Aggressive behavior was significantly lower in the experimental than in the control group, boys being significantly more aggressive than girls in the latter group. This research indicates that experiences of collaborating, feeling emotional security and attaining moments of mindfulness favored the emergence of intrinsic altruism beyond reputation and reciprocation. These results are in line with our hypothesis that altruism is an embodied and situated human capacity, highly susceptible to social influence.

Cognition, Behavior, and Memory
Poster Number 91 / Session II

The impairment in memory reconsolidation induced by IL-1beta is mediated by a decrease of glutamate release and zif268 expression and α-MSH reversed these effects.

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The immune system plays a central role in modulating learning, memory and neural plasticity. Interleukin 1β (IL-1β), a pro-inflammatory cytokine, significantly affects several cognitive processes. Previous studies of our group have demonstrated that the intrahippocampal administration of IL-1β impairs reconsolidation of contextual fear memory. This effect was reversed by the melanocortin alpha-melanocyte-stimulating hormone (α-MSH), through activation of MC4-R. The mechanisms underlying the effect of IL-1β on memory reconsolidation have not yet been established. Thus, we examined the effect of IL-1β on glutamate release and zif268 activation during reconsolidation. Here we found that IL-1β produced a significant decrease of glutamate release after reactivation of the fear memory and also reduced zif268 expression in the hippocampus. The central administration of the α-MSH can reverse both the decrease of glutamate release and zif268 expression induced by IL-1β. Our results establish for the first time the possible mechanisms involved in the detrimental effect of IL-1β on memory reconsolidation and also that α-MSH may exert a beneficial modulatory role in preventing IL-1β effects.

Cognition, Behavior, and Memory
Poster Number 92 / Session III

Memory traces compete under regimes of limited Arc protein synthesis: Implications for memory interference

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Recently encoded information can be lost in the presence of new information, a process called 'retrograde interference'. Retrograde interference has been extensively described for more than a century; however, little is known about its underlying mechanisms. Different approaches agree on the need of the synthesis of plasticity related proteins (PRPs) to consolidate a long-term memory (LTM). Our hypothesis is that when PRPs are limited, interference of a task over LTM formation of another may be due to the utilization of protein resources common to both tasks. Here, by combining the tasks of inhibitory avoidance (IA) and open field (OF) exploration in rats, we show that memory traces compete for their stabilization if PRPs are limited. As a result, LTM is formed for only one of the tasks with a consequent decrease in the memory for the other. Furthermore, infusing Arc antisense oligonucleotide into the dorsal hippocampus, we found that Arc is necessary for LTM formation of these two types of learning tasks and is one of the PRPs that can be shared between them when animals are trained in both OF and IA. In sum, these findings suggest that under conditions of reduced protein availability, a learning task interferes with LTM formation of another by using the available PRPs.

Cognition, Behavior, and Memory
Poster Number 93 / Session I

Research project: role of striatal cholinergic interneurons in the development of motor, social and habit related behaviors

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Tourette syndrome (TS) is a neuropsychiatric disorder characterized by tics and a high incidence of comorbid attention-deficit hyperactivity disorder and obsessive–compulsive disorder. The basal ganglia are key for initiation and coordination of sequential motor actions, procedural learning and habit formation, functions altered in the mentioned disorders. The striatum is the main input nuclei of information to the basal ganglia and its physiology is tightly regulated by local interneurons. Cholinergic interneurons (CIs) can signal the occurrence of behaviorally relevant stimuli. Interestingly, decreased number of CIs has been reported in the striatum of individuals with TS. To elucidate the behavioral impact of striatal CIs reduction we will selectively ablate CIs by using Cre-loxP transgenic mice. We established a new mice line by crossing a cholinergic specific Cre line with a Cre-inducible-diphtheria toxin receptor strain. CIs ablation can be achieved upon local administration of diphtheria toxin. Preliminary results show a marked decrease in the number of striatal CIs in diphtheria toxin treated mice compared with solvent injected ones. We are currently beginning to explore the behavioral impact of such lesions focusing on motor, social and habit related phenotypes

Cognition, Behavior, and Memory
Poster Number 94 / Session II

Increased ethanol self-administration in developmentally low-level lead exposed rats: voluntary intake vs. operant conditioning

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Several evidences demonstrate an interaction between lead (Pb) and drugs of abuse, particularly ethanol. This study aimed to investigate the influence of perinatal low-level Pb exposure on the motivational properties of ethanol by using a two-bottle ethanol/water test and an operant oral ethanol self-administration task. Thirty-five day-old male pups perinatally exposed to 220 ppm Pb were evaluated in their ethanol intake in a free-choice limited paradigm (2 h) at increasing ethanol concentrations (2-10%). Another group of animals was trained to associate the contingency of a lever press with 10% ethanol administration under a fixed-ratio 1 (FR 1) schedule of behavior, which was increased progressively across sessions to FR2, 5, 10, and 20. The results demonstrated that Pb-exposed rats voluntarily consumed more ethanol than their respective controls. Interestingly, the amount of ethanol ingested was sufficient to induce hyperlocomotion, as assessed immediately after the last ethanol (10%) intake session. We also demonstrated that Pb-exposed animals worked harder than the controls to obtain ethanol, evidencing a “break point” at higher lever-press rates. These results are indicative of higher ethanol reinforcing properties in low-level Pb exposed rats as compared to controls.

Cognition, Behavior, and Memory
Poster Number 95 / Session III

Dissociating long term memory storage from expression: an optophysiology approach in the crab Chasmagnathus.

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The canonic view for amnesias suggests storage or, alternatively, retrieval impairments. However, results in our group have shown that some experimental amnesias cannot be explained by these views. Instead, they are explained as a deficit in memory expression (i.e. the memory is stored and can be reactivated but it's not expressed). Here we introduce an approach in achieving neural related evidence for this Hypothesis: we propose that memory storage and expression are different attributes of memories that could be based in different neural interactions. We have made in vivo calcium imaging in Chasmagnathus´s Lateral Protocerebrum (a neuropil proposed to be involved in sensory integration and memory process) and we analyzed whether the induced changes in neural activity correlate with memory expression (during training and 30 minutes after). Then, we tested whether two kind of amnesic treatments, one proposed to interfere with the expression of memories and the other proposed to interfere with memory storage, differentially affect the plastic changes induced by the training protocol. Our results suggest that the changes induced in the neural networks of the Lateral Protocerebrum reflect, at short term, long term memory storage but not long term memory expression.

Cognition, Behavior, and Memory
Poster Number 96 / Session I

Neurobiology of decision making: a dual choice paradigm in the crab Neohelice granulata

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Simple perceptual tasks have laid the groundwork for understanding the neurobiology of decision-making. Decisions between two choices in a perceptual-motion task demonstrate mechanisms of decision-making. In Neohelice, differences in the latency, intensity and probability of escape side were found between lateral and dorsal looming stimuli. For the dorsal looming, escape side is unpredictable, which offers the opportunity to investigate the neurobiology of a dual choice in the crab. Here we show not only the direction of escape is highly determined by the direction of the object approach, but also the visual context in which the stimulus is presented. Upon repeated stimulus presentations of the dorsal looming, each individual repeats the same escape direction. We started exploring whether these persistent responses could be changed through an instrumental conditioning, where the first choice in the escape side was punished. Together with this behavioral results we began investigating the neuronal mechanisms involved in such decision making processes, which to a large extent are thought to take place in a group of identified giant neurons of the crab's brain.

Cognition, Behavior, and Memory
Poster Number 97 / Session II

Neural activation of several areas of the telencephalon in toads (Rhinella arenarum) for a passive avoidance task

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Previous studies in toads indicate that saline NaCl solutions yield incentive values ranging from appetitive (where toads approach hypotonic or slightly hypertonic solutions lower than 200 mM, leading to weight gain), to neutral (300 mM slightly hypertonic solution, leading to no net weight gain or loss), and to aversive (where toads escape from highly hypertonic solutions higher than 400 mM, leading to weight loss). Two groups of toads were trained in a one-way shuttle box with two compartments: one lighted and another darkened. Animals began their sessions in the lighted compartment. Since toads have a natural preference for dark places, during the first sessions they jumped to the dark compartment. There, one group received an 800 mM solution and the other a 300 mM solution. After 10 sessions, latencies in the group 800 increased significantly. When training ended, animals were sacrificed and their telencephalon processed with a silver nitrate technique (AgNor) in order to identify brain active nuclei. Results showed an increased activity in the striatum of the toads in group 800. These findings provide initial information about the neural circuit engaged in passive avoidance learning, a situation modeled after one extensively used to study fear conditioning in mammals.

Cognition, Behavior, and Memory
Poster Number 98 / Session III

Ethanol-mediated flavor conditioned preference utilizing a voluntary and intermittent consumption schedule in adolescent rats

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We aimed to develop a conditioned flavor preference paradigm mediated by ethanol. We paired a flavor with ethanol (5% v/v) employing a voluntary and intermittent consumption schedule. Adolescent male Wistar rats (PD28) remained with free access to food and water during training. At the moment of preference test, animals were water deprived for 20 hours. Subjects were exposed to Almond or Banana, sweetened with saccharin on alternate days. One flavor was presented with ethanol (CS+), while the other one was presented in absence of the drug (CS-), flavors acting as CSs counterbalanced. Across 40 days of conditioning, consumption levels and preference for the CS+Ethanol solution (in comparison with water intake) were significantly higher than those of the CS-. However, the preference for the CS+ over the CS- was not evident during the test. When data were analyzed in terms of sequence of flavor presentations, we observed a nearly significant higher consumption of Banana acting as CS+ (signaling ethanol) than when this flavor acted as CS-. For Almond this trend was not evident. Even when more studies are needed, these results suggest that ethanol may act as a positive reinforcer, allowing a conditioned flavor preference.

Cognition, Behavior, and Memory
Poster Number 99 / Session I

EFFECTS OF MIDAZOLAM AND PROPRANOLOL ON FEAR MEMORY RECONSOLIDATION IN ETHANOL DEPENDENT RATS

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Withdrawal from chronic ethanol (ETOH) facilitated the formation of contextual fear memory which is resistant to extinction. Here we examined the effect of post-reactivation amnestic treatments such as Midazolam (MDZ) and Propranolol (PROP) on fear memory reconsolidation in ETOH dependent rats. Male Wistar rats made dependent via an ETOH containing liquid diet for 14 days. Contextual fear conditioning was performed 3 days after withdrawal. The next day, rats received an intraperitoneal injection of MDZ (3mg/kg) or PROP (10mg/kg) immediately after 3 or 5 min reactivation session, respectively and the freezing response was evaluated 24 h later. Neither MDZ nor PROP decreased freezing levels in ETOH dependent rats. In contrast, both drug treatments induced an effective attenuation of fear response in control rats. This effect lasted up to one week. Our findings suggest that previous history of ETOH dependence/withdrawal lead to the generation of memory traces less vulnerable to disruption after recall.

Cognition, Behavior, and Memory
Poster Number 100 / Session II

Down regulation of the oncogene Shp2 delays aging

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Aging in multicellular organisms it is characterized by accumulation of damage in macromolecules, which consistently it is associated with a decline in a variety of physiological and behavioral functions. Interestingly, the mechanisms involved in aging and cancer appear to be opposing each other. Among the age-related declines, memory impairment is one of the most disturbing alterations. Strikingly, the onset of the age-related memory impairment seems to be independent of reactive oxygen species, the main and best characterized factor leading to aging. The oncogene Shp2, a protein tyrosine phosphatase involved in leukemia in a number of conditions, including Noonan syndrome, regulates positively several growth factor receptor. Previously, we have detected that the overexpression of Shp2 protects against thermal stress, however, its role in aging it is unknown. Several methodologies to measure and analyze aging are in use; however, they do not work satisfactorily under different conditions and does not describe properly many important features of aging. Here we present a method of automatization to analyze motor and cognitive aging as well as preliminary studies on the effects of the genetic manipulation of Shp2 on motor and cognitive aging in a Drosophila model system.

Cognition, Behavior, and Memory
Poster Number 101 / Session III

Game theory and cognitive skills: a study of the ability of backward induction

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Backward induction (BA) is the process of reasoning backwards in time, from the end of a situation or a problem to determine an optimal sequence of actions. Rustichini and others discussed this skill using "the race game". This game is a zero sum game, for two players with perfect information. In their work show that this game is a BA. In another work by Burks - Carpenter - Goette - Rustichini, the authors analyze the relationship between the development of certain cognitive skills and individual economic preferences. In their paper they conclude that taking better decisions about the economy and finance, are those who have obtained better scores on cognitive tests, particularly in "the race game". Using "the race game" to study this ability, our work is focused on the following objectives: -Understand the temporal evolution, according to the ages of players, of this skill. -Detect significant/qualitative changes of the ability to BA, and critical parameters in which these are produced (number of trials, age, previous eductation, or others) -Analyze how changes in the presentation of the game affect the detection of the optimal strategy of play, and how these changes are related to the knoweledge generation. -Identify and understand which strategies individuals use to play (not necessarily the optimal) and the algorithms associated. In particular, analyzed mathematically, with tools of game theory classical, and then in the experiments, suboptimal strategies.

Cognition, Behavior, and Memory
Poster Number 102 / Session I

Long-term effects of chronic aerobic exercise on object recognition memory in rats.

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Moderate exercise produces a great benefit on brain health and behavior. The objective of the present study was to investigate the effects of chronic aerobic exercise on age-dependent cognitive decline that may occur independently and in parallel with changes in hippocampal function in rats. We designed an aerobic training program with the treadmill running following the basic principles of human training, and assuming that rats have the same physiological adaptations. The discriminative ability to detect non spatial changes (substitution of a familiar object with a new one), and spatial changes (displacement of a familiar object) were studied in middle age (8 months) and old age rats (18 months) with standard spontaneous object recognition procedures. Trials consisted of 3 consecutive days of habituation in the Open Field, followed by sample and choice phases, separated by 24 hs of delay. Trained rats, regardless of age, showed greater exploratory activity in both phases. Middle age exercised rats showed greater discriminative response to novelty. However, old rats, regardless of exercise, had no differences in this parameter. In contrast, related to spatial and contextual changes, the greatest long-term effects of exercise on hippocampus-dependent spatial memory, were detected in old runners. We conclude that long-term, regular aerobic exercise has a positive impact on non-spatial and spatial components of declarative memory, especially in old rats.

Cognition, Behavior, and Memory
Poster Number 103 / Session II

Reactivation conditions are critical to permanently reduce a fear memory through the

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Monfils et al (2009) developed a drug-free behavioral approach to permanently modify fear memories: applying extinction training during the labile or destabilized phase of a reactivated memory. The procedure prevents spontaneous recovery, reinstatement or renewal. However, some researchers couldn't replicate these findings, but never probed to destabilize the memory. Given that not all reactivations destabilize a trace, we try to find if this is critical to the reactivation-extinction procedure. With a contextual fear paradigm in rats, we determine reactivation conditions that could destabilize the trace. Using the amnestic benzodiazepine Midazolam (MDZ) (3 mg/kg), we found that 1 min. reactivation can't destabilize the memory. 3, 4 or 5 min. actually destabilized the trace (MDZ reduced freezing compared to saline controls). Actually, 4 min. lead to the deepest MDZ effects. Then we try to determine if extinction after 1 or 4 min. reactivations would produce differential effects. We trained two groups and applied extinction to only one. Extinction group expressed less fear than control in a 24 hs post extinction test but spontaneous recovery was observed one week later. A similar pattern was observed with a 1 min. reactivation prior to extinction. However, when a 4 min. reactivation preceded extinction, spontaneous recovery didn't occur. These results cannot be explained on the amount of extinction, since a total of 15 min. was always used (0-15, 1-14 and 4-11).

Cognition, Behavior, and Memory
Poster Number 104 / Session III

Involvement of NMDA receptors in the acquisition of contextual fear memory in preweanling and weanling rats trained in the CPFE paradigm

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The capability to acquire contextual fear learning emerge around weanling in rats, and that this capability is NMDA-type glutamate receptors (NMDAr) dependent. A recent study using the Context Preexposure Facilitation Effect procedure demonstrated evidences of contextual fear conditioning in preweanling rats. Additionally, it was observed that preweanling and weanling rats trained with an immediate-shock procedure showed evidences of fear conditioning. In this study the observation of contextual fear conditioning at this age was facilitated by the temporal analysis of multiple behaviors. The aim of this study was to study the involvement of the NMDAr in the acquisition of contextual fear in weanling and preweanling rats and to evaluate their involvement in fear conditioning induced by an immediate-shock procedure. Results obtained in these experiments showed that contextual fear memory is NMDAr-dependent at both ages. The behavioral pattern expressed by preexposed subjects treated with MK-801 during the preexposure phase was identical to non-preexposed rats. Finally, fear memory induced by the immediate-shock treatment was not affected by the administration of MK-801. We conclude that NMDAr modulate the acquisition of contextual fear conditioning in preweanling and weanling rats.

Cognition, Behavior, and Memory
Poster Number 105 / Session I

Mossy Fiber Synaptogenesis after Spatial Water Maze Overtraining and its Functional Implications for Information Processing in the Hippocampal Network.

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Spatial water maze (WM) overtraining in rats induces hippocampal mossy fiber synaptogenesis in the CA3 Stratum Oriens. We hypothesized that these structural changes have important implications for hippocampal information processing. By using compartmental analysis of temporal activity with fluorescence in situ hybridization (catFISH) for the immediate early gene Arc, we characterized pattern separation and pattern completion properties of CA1 and CA3 hippocampal networks in animals that underwent WM overtraining compared to swimming and intact controls. We found that both, swimming and WM treated animals improved pattern completion and separation properties in contrast to intact controls. This was later corroborated behaviorally with a delay non-matching to place task. Currently we are determining whether or not this improvement in statistical pattern comparison correlate with the structural changes in the connections between the dentate gyrus and CA3 in the hippocampus. We will also present preliminary results from experiments designed to determine if the neurons that present the increased density of synapses are the same neurons recruited by the behavioral experience that previously induced this structural synaptic changes.

Cognition, Behavior, and Memory
Poster Number 106 / Session II

The role of hippocampal adult neurogenesis in information processing

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The functional role of hippocampal dentate gyrus (DG) adult neurogenesis in information processing is a fundamental question. We approached this issue by detecting the expression of the immediate early gene Arc in adult-born neurons in response to behavioral experiences. We have found that new neurons develop a specific Arc-expression response to spatial exploration when mature. This specific response to spatial exploration is observed since neurons are 30 days old, which is congruent with the time these neurons reach cellular maturity. By using the probability of response at different times throughout the life of these neurons, we had proposed a mathematical model suggesting that after 301 days old adult born neurons are unlikely to respond to exploration. The model also predicts that in a 7-month-old rat the majority of the DG neurons that respond to exploration must have been born during adulthood. Interestingly, while still immature, these cells contribute with at least 50% of the spontaneous activity in the DG network. We can interpret this spontaneous activity as noise, and we propose that this noise may also be required to properly process behavioral information, by providing stochastic resonance to the DG network. Finally, by characterizing the Arc-expression response of these new neurons to object recognition, we have found evidence that their involvement in this task differed from its involvement in spatial information processing.

Cognition, Behavior, and Memory
Poster Number 107 / Session III

Timbre attributes of saxophone multiphonics: psychophysical and spectral analysis

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Timbre is a multidimensional attribute of sound. In many cases is useful to distinguish one musical instrument from other or to categorize the vowels and consonants. In this work we studied the timbre of saxophones multiphonics, a set of sounds that could be created with a saxophone that have the characteristic of having more than one identifiable pitch, instead of standard playing notes. The timbre of this sounds are rather heterogeneous and this is related with the problem of timbre classification and timbre similarity evaluation. For this purpose we implement a pair comparison test for evaluating the similarities within a group of 15 multiphonics. The results were analysed by multidimensional scaling and showed that the sound are grouped in different classes in accordance to the saxophone execution technique.Finally the psychological dimension that arise with the multidimensional scaling were correlated with physical sound parameters as the spectral content and modulation index.

Cognition, Behavior, and Memory
Poster Number 108 / Session I

Acute ghrelin administration reverses the memory impairment induced by bilateral olfactory bulbectomy in mice

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This study aims to examine the effects of gherlin (Ghr) a hormone synthesized predominantly by gastrointestinal endocrine cells and released during periods of negative energy balance, on memory impairment induced by bilateral olfactory bulbectomy, a well established animal model of depression. In a previous work we demonstrated that Ghr 0.3 nmol/µl, produced antidepressant-like effect and reversed OB-induced depressive-like behavior. Adult male Albino's Swiss mice were divided in two groups: without bulbectomy (Sham) and bulbectomized (OB). Both groups were cannulated intracerebroventricularly and seven days after, the memory performance was evaluated using the object recognition test. The animals were infused with saline or Ghr 0.3 nmol/µl immediately after training (n=10 animals/group). The OB animals infused with saline (OB-S) showed a decrease in the time of novel object exploration in relation to Sham animals indicating memory impairment ($F=15.62$, $df=1$, $p \leq 0.05$). When Ghr was administrated to OB, the memory retention increased in relation to OB-S mice, reaching a performance similar to Sham animals ($p \leq 0.05$). In conclusion, these results provide clear evidence that the acute Ghr administration reverse the memory impairment induced by bilateral olfactory bulbectomy in mice.

Cognition, Behavior, and Memory

Poster Number 109 / Session II

Synaptic NF-kappa B localization dynamics in learning and memory

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NF-kappa B activation has been shown to be necessary for long-term memory consolidation in the mouse inhibitory avoidance learning paradigm. NF-kappa B is activated in the nucleus of hippocampal cells in a specific temporal window during consolidation. Previous results showed that the transcription factor is also present in synaptic terminals. More importantly we found NF-kappa B strongly bound to membranes of these terminals. This new finding poses the question, is there a local role for NF-kappa B? And if so, is it essential for learning and memory? Another pool of NF-kappa B has been found in the synaptosomal content, and its activation measured through Electro Mobility Shift Assays (EMSA) is modified during consolidation of shocked mice, when comparing to naïve and unshocked. The membrane bound NF-kappa B increases 5 minutes post training only in shocked mice. The re localization of the transcription factor could implicate a new function of NF-kappa B that might intervene in the consolidation process. The aim of this research is to study the dynamics of synaptic NF-kappa B activation during consolidation, discussing the novel localization of the transcription factor in membranes of synaptic terminals.

Cognition, Behavior, and Memory
Poster Number 110 / Session III

Epitastic genes of the Noonan syndrome allele cswN308D produce learning impairment in Drosophila

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Learning disability is a common cognitive alteration in a group of disorders in which a higher activity of the Ras/mitogen-activated protein kinase (MAPK) signaling pathway is a hallmark. This group of genetic disorders, including Noonan syndrome, are caused by mutations in genes encoding for components of the Ras/MAPK signaling pathway. Recently, we identified that different csw gain-of-function alleles, including the cswN308D which models the commonest Noonan syndrome mutation, impair a fundamental property of learning called the spacing effect (SE). The SE makes reference to a longer-lasting memory induced by spaced experiences over time (spaced training) compared with experiences in close temporal proximity (massed training). Importantly, by analyzing ectopic wing vein phenotypes in Drosophila, we previously indentified that several genes, including RAS, Notch and STAT, interact genetically with the cswN308D allele. Here we present preliminary studies on the effect of enhancing or suppressing the activity of genes that interact genetically with the allele cswN308D (i.e. RAS, Notch and JAK/STAT) on learning in a Drosophila model system. These studies will be useful in future experiments to analyze whether those genes are involved in the control of the SE.

Cognition, Behavior, and Memory
Poster Number 111 / Session I

The effect of stimuli discrimination and priming in a equivalence relations

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In this study was to replicate the priming effect in the equivalence relations observed in the study conducted by (Barnes-Holmes), but using an SOA greater than 900 ms., and to study the effect of the ease of discrimination of stimuli in the equivalence relations and the possible effect on priming. In the first experiment we trained two equivalence classes for three stimuli in a matching to sample without delay. In both experiments we used as stimuli non words chosen for their phonetic frequency; however, only in the first experiment were these words difficult to discriminate. The training was similar in all the experiments, where we used two classes of tree elements in three blocks of training. Next, the subjects completed a priming test in which the stimuli were presented as target-priming words in three forms. First experiment: only two out of the ten subjects that were evaluated passed the criterion of tests in the equivalence relations. On the other hand, we found no priming effects on the priming test in reaction times (F(0,098)=1, 8, p> 0,022) and error rate (F(3,359)=1, 8, p= 1). Second experiment: five out of nine passed the criterion of tests in the equivalence relations. In this case we found priming effects on the priming test, in the Error Data (F(3,404)=1, 7, p

Cognition, Behavior, and Memory
Poster Number 112 / Session II

Freedom and rules in human sequential performance: a refractory period in eye-hand coordination

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In action sequences, the eyes and hands ought to be coordinated in precise ways. The mechanisms governing the architecture of encoding and action of several effectors remain unknown. Here we study hand and eye-movements in a sequential task in which letters have to be typed while they fall in the screen. We observe a strict refractory period of about 200 ms between the initiation of manual and eye movements. Subjects do not initiate a saccade just after typing and do not tap just after making the saccade. This refractory period is observed ubiquitously in every subject, in each step of the sequential task, even when taps and saccades correspond to different items of the sequence, for instance when a subject types a letter which has been gazed in a preceding fixation. These results extend classic findings of dual-task paradigms, of a bottleneck tightly locked to the response selection process, to unbounded serial routines. Interestingly, while the bottleneck is seemingly inevitable, better performing subjects can adopt a strategy to minimize the cost of the bottleneck overlapping the refractory period with the encoding of the next item in the sequence.

Cognition, Behavior, and Memory
Poster Number 113 / Session III

NMDA receptor subunits involvement in memory formation of hippocampus-dependent tasks

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Hippocampal NMDA receptors (NMDAR) are required to consolidate inhibitory avoidance (IA) and open field (OF) memory in rats, since the administration of MK-801 immediately after training leads to amnesia. Most hippocampal NMDAR contain GluN2A or GluN2B subunits. The selective GluN2B antagonist Ifenprodil administered intra-hippocampus immediately after training, allowed long-term memory (LTM) formation of IA with a subthreshold training, facilitated memory of IA when training was just overtreshold and of an object location task. These results indicate that GluN2B-containing NMDAR negatively modulate memory consolidation. On the other hand, habituation to an OF was not affected by ifenprodil injected intrahippocampus right after the first session, suggesting that it does not depend on GluN2B containing receptors. Hippocampal proteins obtained 30 and 70 minutes after rat exposure to a 5 minutes OF session – which leads to recognition and habituation to the field - were analyzed by westernblot for NMDAR subunits. While GluN1 and GluN2A significantly increased at 70 min, GluN2B did not. Our results show that NMDAR subunits actively and selectively change during OF consolidation, in a similar way to the changes reported to occur after LTP induction (see Cercato et al; Aguirre et al, 2012). These changes, along with the above reported behavioral data, suggest that GluN2A rather than GluN2B would participate in the OF memory (spatial habituation) processing.

Cognition, Behavior, and Memory
Poster Number 114 / Session I

Inflation of subjective perception in peripheral vision

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There is a compelling subjective impression that peripheral vision is colorful and vivid. However, peripheral vision is characterized by carrying less information than foveal vision: it is associated with low spatial resolution, low color sensitivity and in general receives little attention compared to the foveal location. it is not clear if the physiology of the retina and the wiring of its input to the primary visual cortex can afford such details of processing. It seems likely, as in the case of Rahnev et al. (2011), that some similar subjective inflation is at work for peripheral vision. We investigate this possibility in a psychophysical experiment using a detection task. We found that subjects tend to use a more conservative detection criterion at the center than at the periphery (that is, subjects reported seeing the target more frequently in the periphery). These results are explained with a model in which the trial-by-trial variability of the perceptual signal is larger at the periphery than at the center. A more detailed model relates the difference in the variance of the perceptual signal with the fact that central vision allocates more neuronal resources than peripheral vision. These findings may partially reflect our impression of 'seeing' the whole visual scene despite our limited processing capacity of peripheral stimuli. Rahnev et al. (2011). Attention induces conservative subjective biases in visual perception. Nature neuroscience 14(12), 1513–5.

Cognition, Behavior, and Memory
Poster Number 115 / Session II

Influence of two-dimensional sonic crystal on auditory depth perception for pink noise filtered bands

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There are a number of cues that the human auditory system uses that result in a perception of depth for an acoustical source. The most prominent is intensity level at the position of the listener. Other cues include the energy ratio between direct and reverberant sound (D/R ratio), the spectral content and dynamical and binaural cues. Among binaural cues, interaural cross-correlation (IACC) provides a cue of depth because this magnitude is much higher for the direct sound than for the reverberant field. In this work, we study how intensity, D/R ratio and IACC cues can be modified by purely acoustic means for a particular sound field: the transmitted field of an acoustic source through a sonic crystal (an acoustic metamaterial formed by an array of rigid cylinders in air), and how these changes can affect the perception of depth. Human participants underwent an experiment in a virtual environment to evaluate the acoustic depth for pink noise filtered bands passing and not passing through a sonic crystal for several frequencies and listener positions. We show that the presence of the sonic crystal slab have a noticeable effect on the auditory depth perception and we are able to determine the relative influence of intensity, D/R ratio and IACC on that percept.

Cognition, Behavior, and Memory
Poster Number 116 / Session III

Muscarinic antagonism during consolidation disrupts long-term memory expression without affecting memory storage

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Until now, most works on induced amnesia in animal models interpreted deficits in memory expression as deficits in the storage or retrieval of memory. We proposed that during consolidation, acquired information is evaluated and that during this process it is decided whether the new memory is going to be expressed or not in the long-term. A protocol to test whether a non-expressed memory trace is indeed an intact functional memory that can be retrieved -even when is not expressed- is to prove that this memory is able to enter in reconsolidation. For this purpose, a reminder is presented followed by a facilitatory treatment that changes long-term memory expression. Very acute controls for memory reconsolidation are needed to discard another effects related to reminder presentation, as summation of new memories. We found that the amnesic effect of pre- and post-training scopolamine (SCP, a competitive muscarinic receptor blocker) injections can be reversed by improving memory reconsolidation. This reversion depends not only in the presentation of a reminder, but also this reminder must be able to trigger reconsolidation, thus ruling out summation effects. On the contrary, higher doses of SCP or sulfazalazine (that induces amnesia by reducing the entrance to the nucleus of NF-κB transcription factor) induce amnesias that can not be reverted by this protocol, thus showing that storage of memory or the formation of retrieval links could have been disrupted by those treatments.

Cognition, Behavior, and Memory
Poster Number 117 / Session I

Spatial novelty promotes the persistence of memory

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The molecular mechanisms that make some long-term memories (LTM) last longer than others are not totally clear. Our previous works showed that persistence of LTM storage requires a late protein synthesis-dependent phase in the hippocampus depending on activation of VTA/hippocampus dopaminergic connection. Nevertheless, little is known about the effect of new information acquisition during this critical time window. Here, we demonstrate that exposure to a novel environment (an open field, OF) 11h after a weak inhibitory avoidance training (IA) promotes this memory trace 7 days, but not 1 day after training. The exposure to a novel OF in different times post training does not affect the retentions of IA memory. However, this facilitatory effect is absent when the OF is familiar. In addition, when OF memory formation is blocked by intra-hippocampus infusion of an antisense oligonuceotides of arc –an immediate early gene implicated in synapses modeling -, the effect of the exploration of the novel OF on LTM persistence of IA training is completely prevented. Based on these results, we suggest that IA long-lasting memory can be promoted by exposure to a novel environment 11h after IA training possibly modulating dopamine release and protein synthesis.

Cognition, Behavior, and Memory
Poster Number 118 / Session II

Modulation of adult neurogenesis by spatial learning

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Adult neurogenesis occurs in the hippocampus and olfactory bulb and it is modulated by several physiological and pathological conditions. In this study we aimed to investigate how hippocampus-dependent spatial learning modulates the development and functional integration of adult-born dentate granule cells (GCs). A retrovirus expressing GFP was delivered to the dentate gyrus to label newly generated GCs. Two weeks later mice were exposed to the Morris Water Maze. Morphology and expression of neuronal markers was analyzed in newly generated GCs after training and probe testing, performed at 27 days post infection). Interestingly, while dendritic tree length remained unaltered, dendritic spine density was reduced in mice exposed to water maze learning. This reduction in glutamatergic connectivity might respond to the refinement of afferent connections in neurons involved in the learning process. We are currently investigating the effects of spatial learning on the integration of four week old neurons, which are highly excitable and might be highly involved in demanding cognitive tasks.

Cognition, Behavior, and Memory
Poster Number 119 / Session III

Savings measured after eliminating aftereffects, underestimate the rate of readaptation

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The formation of a sensorimotor memory after motor adaptation is reflected in the occurrence of after-effects, memory retention and an increase in the rate of re-learning (savings). A typical savings protocol involves one session of adaptation followed by a sufficient number of null trials to bring error down to baseline levels (washout) and, subsequently, a second session of adaptation. The rationale for the washout is to equate initial error levels across learning and re-learning sessions to accurately estimate savings (1). The current literature on the occurrence of savings in motor adaptation is equivocal (e.g. 2). One possible explanation inspired in the phenomenon of extinction in classical conditioning (3), is that washing out behavioural gains may mask the expression of the sensorimotor memory formed during adaptation. To test this hypothesis, we conducted two experiments. Experiment 1 showed that inserting a 24 h interval between washout and re-learning increased the amount of savings. This finding is consistent with extinction in classical conditioning. Experiment 2 revealed that this phenomenon takes place in the primary motor cortex. Ref. 1. Zarahn et al. J Neurophysiol (5):2537-48, 2008. 2. Kojima et al. J Neurosci 24: 7531-7539, 2004. 3. Rescorla. Spontaneous recovery. Learn Mem 11:501-509, 2004.

Cognition, Behavior, and Memory
Poster Number 120 / Session I

Memory interference in an object-recognition learning task depends on the features of the interpolated experience.

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Recently encoded information can be lost in the presence of new information, a process called 'retrograde interference' (RI). Based on our recent findings on RI using a spatial task in combination with an aversive task (Martínez et al., 2012); here, we studied if RI could occur using only non-aversive tasks. Derived from object-recognition paradigms, we designed a training protocol consisting of two different learning sessions (called "tasks") and evaluated the long-term memory (LTM) of each task 24 h after the training. The aim of this work is to analyze which aspects of the second task are related to the occurrence of RI in the consolidation of the first task trace. In particular, we evaluated the effect of the context and the objects whether they are novel or familiar and the influence of the interaction between them. Besides, we studied the involvement of the hippocampus and the medial Prefrontal Cortex in the consolidation of these tasks. Our results show that the degree of novelty experienced in the second task is relevant for RI and that these brain regions are implicated in the formation of the object recognition LTM.

Cognition, Behavior, and Memory
Poster Number 121 / Session II

Identification of target genes downstream of the Nuclear Factor-kappa B transcription factor involved in recognition memory formation.

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Nuclear factor kappa B (NF-kB) is a transcription factor that plays a key role in the activity-dependent neural plasticity involved in memory formation. In this work, we focused our interest in downstream genes up-regulated by NF-kB during memory consolidation. We studied two genes, zif268 and bdnf, as potential targets for NF-kB direct transcription regulation during novel object recognition (NOR) memory consolidation in the mice hippocampus. zif268 is an immediate-early gene that codes for the transcription factor ZIF268. bdnf codes for the brain derived neurotrophic factor (BDNF) which is secreted locally at the synapse in response to neuronal activity. Both proteins have been widely implicated in memory. Our results indicate that ZIF268 protein levels have a fast and transient increase forty five minutes after training returning to baseline three hours later. This increase was significantly reduced when an NF-kB inhibitor was injected immediately after training. Conversely, BDNF levels were not modified by training at any time point studied. These results support that the transcription of the zif268 gene is being regulated by NF-kB during NOR memory consolidation, while ongoing experiments are being performed to assess possible changes for the bdnf gene at the level of mRNA.

Computational Neuroscience
Poster Number 122 / Session III

Unsupervised automatic analysis of discourse for psychosis diagnosis

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Mania and schizophrenia are mental disorders that produce alterations in cognitive behavior. Standard psychiatric scales are based on assessments of interviews with patients. Automatic speech processing using natural language processing tools open a new perspective for diagnosis of psychosis. We analyse reports of dreams produced by schizophrenic and manic patients, and automatically classify into groups of people according to their psychiatric characteristic. We measure topological characteristics of the word graph of the report (e.g. diameter, numbers of loops) and combining this information with semantic analysis measures like Latent semantic analysis (LSA), Google Similarity Distance and grammatical tagging techniques, we outperform the standardized psychiatric scales classifying correctly more than 83% of patients. These results suggests that unsupervised automatic strategies of speech analysis may be feasible for support to physicians in mental disorder diagnosis.

Computational Neuroscience
Poster Number 123 / Session I

Computational influence of neurogenesis in the processing of spatial information in the dentate gyrus

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The objective of this study is to analyse the effect of hippocampal neurogenesis on the spatial maps of granule cells. To this end, we developed and improved an artificial neural network proposed by Aimone in which many biological processes were included, so that the results had a greater biological plausibility. We proposed a new paradigm of learning-testing to analyse the activation of encoding place cells across contexts over time in the dentate gyrus. We found that, even though the neurogenesis was present, the quantity and morphology of the place fields continued to be expressed the same way on the granule cells. Additionally, we observed that neurogenesis was a good mechanism for reducing the rate remapping that took place in the place fields of the granule cells.

Computational Neuroscience
Poster Number 124 / Session II

Information Theory approach to characterize the internal structure of the rhythmic oscillation patterns

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The classical point of view is that neurons transmit information exclusively via modulations of their mean firing rates, however it is well established that neurons can fire spike patterns with a few milliseconds of temporal precision. To gain a better understanding of how information is transmitted in the brain we need therefore to learn how characterize first the fine temporal structure of complex neuronal signals not just using the probability distributions associated with inter-spike intervals, but also using much more subtle measures which could account for its causal structure. In this work, we use an Information Theory measure to characterize the self-sustained rhythmic oscillation of a minimal model simulating the neural spiking activity

Computational Neuroscience
Poster Number 125 / Session III

Massive-scale educational intervention: Mate Marote goes to La Rioja

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Argentina is living a unique oportunity where a great amount of primary and secondary school students have their own laptop, given by institutional programs such as Joaquín V. González (Primary school at La Rioja). The fact that all learning and teaching tasks are represented in the same digital environment is a formidable tool for educational applications, as well as for research and experimentation. From the perspective of information technology, the challenge is how to interface with this vast corpus of cognitive development data to convert conceptual questions relevant to educational practice into quantifiable, analytic queries. We designed a flexible framework consisting of educational games and activities, designed for automatic maintenance, keeping up-to-date information of this application and registering anonymous usage behavior for further analysis. The first pilot intervention was deployed in La Rioja, with more than 150 computers installed. This deployment consisted of three games to train cognitive capabilities: mainly planning, working memory and inhibitory control. Interestingly, even though this intervention is unsupervised, preliminary statistic analysis shows that children gaming behavior is consistent with previous supervised-interventions results. This effort suggests a novel window for studying (and intervene in) human cognition development, with a great amount of new possibilities, pushing a profound reformulation of teaching and learning.

Computational Neuroscience
Poster Number 126 / Session I

Modeling gain control in sensory networks: The olfactory case

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The natural stimuli are presented in a large range of intensities. It is important for animals to recognize the stimulus identity independently of it\'s intensity; especially increasing sensitivity when the stimulus is weak and avoiding saturation when it is too intense. This property is named gain control. It allows us to sense the presence of a flavor regardless of its intensity, or an odorant irrespective of the concentration. This last one it is important in particular for bees because during the foraging the odor concentration fluctuates while approaching the targets. The computational models of the Antenal Lobe (AL) are normally based on random connectivity among neurons with specific defined probabilities for the connections between different types of neurons. In order to show gain control properties the probabilities have to meet functional relationships that do not seem to have biological meaning. In the present work we show results using a realistic model that considers our current knowledge of the AL structure. The model considers the glomerular structure and the connections between Projection Neurons and Local Neurons inside them. The neurons activity is calculated using the Hodgkin-Huxley model. Our simulations show that the current model accomplishes gain control properties without requiring specific functional restriction in the connection probabilities between neurons. The new model is more robust for gain control property than previous ones.

Computational Neuroscience
Poster Number 127 / Session II

Maximum entropy constraints on spike correlations in a neuronal ensemble

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The nature of the neural code has been a matter of debate during the last three decades. The sensory information in the brain can be carried by action potentials (spikes), and be packaged, for instance, through a simple counting code, within the temporal structure and / or through the correlations between spikes. In the framework of a perturbative expansion for short time windows, we formally estimate correlations between action potentials for a set of neurons under the principle of maximum entropy. This formalism will allow us to investigate within information geometry the role of fundamental constraints in the neural code when considering short time windows.

Computational Neuroscience
Poster Number 128 / Session III

A biologically inspired robot for visually-guided behaviors

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In this study, we present a biologically inspired robot that can approach a target while avoiding collisions with fixed obstacles. The robot's design is based on neuro-ethological studies of visual behavior of insects and crustaceans. In this poster, we describe: a) a vision system consisting on spherical mirror that provides the robot with a 360 degrees panoramic visual field, b) a vision-based processing algorithm motivated on insects' visual abilities [Horridge, 2005]. c) a biologically inspired control system, that generates the motor commands depending on the visual information adquired. Finally, we analyze the behavior of the robot through computer simulations and robot's navigation measurements in a real environment. Horridge, A. (2005) What the honeybee sees: a review of the recognition system of Apis mellifera. Physiological Entomology (2005) 30, 2-13

Computational Neuroscience
Poster Number 129 / Session I

Active mapping of brain

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This paper develops and tests a theoretical framework for the study of the Nervous Systems (NS). It consists of a mathematical model constructed from a three-dimensional matrix which make it possible to understand the way the Nervous System works by means of the study of input and output channels, instead of acquiring electric signals or using imaging systems on active areas. This model is based on the logic used in the memory of programmable logical devices of different electronic equipments and their associated math, resulting in a simple analysis, possible to be applied in the actual study of the Nervous System.

Computational Neuroscience
Poster Number 130 / Session II

Unsupervised detection of stylistic changes in music history

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The brain processes temporal statistics to predict future events and to categorize perceptual objects. These statistics, called expectancies, are found in music, and span a variety of different features and timescales. Specifically, there is evidence that music perception involves strong expectancies regarding the distribution of a melodic interval within the context of another (Cuddy and Lunney, 1995; Krumhansl, 1995; Schellenberg, 1996). The recent availability of a large western music dataset, consisting of a historical record condensed as melodic intervals counts (Viro, 2011), has opened new possibilities for data-driven analysis of musical perception. In this context, our main contribution is two fold. Firstly, we present a machine learning approach that, based on the aggregated interval statistics for each year since 1700 to 1930, accurately identifies historical trends and stylistic transitions between the baroque, classicist and romantic periods. Secondly, we relate these findings to existing cognitive theories about music expectation.

Motor Systems

Poster Number 131 / Session III

Using a mathematical birdsong model to unveil neural coding in zebra finches

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Songbirds are a well studied example of vocal learning and motor control that allows to integrate neural and peripheral recordings with a precisely quantifiable behavior. We worked with a minimal physical model for birdsong production. To validate this model, we assessed the responses in the premotor forebrain nucleus HVC to song playback in which neurons exhibit highly selective responses to the bird\\\\'s own song (BOS). Remarkably, the mathematical model elicited responses strikingly similar to those for BOS, with the same phasic-tonic features. These results demonstrate that a low dimensional model is sufficient to capture behaviorally relevant features, providing valuable simplification that can help clarify neural coding. Analyzing HVC neurons responses to playback of each bird's own song, we observed that projection neurons were excited and interneurons were suppressed, with near-zero time lag, at particular events of the song unveiled by the mathematical model. In preliminary data, we confirmed these results with HVC recordings in singing birds. Given that HVC activity occurs with near synchrony to behavioral output, we propose that the activity of HVC neurons represents the sequence of particular events in song as a "forward" model making predictions on expected behavior.

Motor Systems

Poster Number 132 / Session I

Unveiling the motor map for vowels and plosive consonants.

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The ability to produce and perceive the different phonemes of a language relies on the capacity of the vocal tract to switch from very different profiles. Since the beginning of linguistics, lot of effort has been put to unveil maps between the anatomical and phonemic spaces. In this work we monitor the dynamics of the upper vocal tract using 3 pairs of hall effect detectors and magnets in the mandible, tongue and lips. From the resulting time signals of every possible combination of vowels and plosive consonants, a binary space for the motor gestures can be reconstructed. The original utterings can be robustly reconstructed for different subjects and recording sessions. Based on such a simple and economic device, we are developing a real-time voice synthesizer from the simple motor gestures generated in normal speech.

Motor Systems

Poster Number 133 / Session II

Commutator for chronic physiological recordings

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The chronic recording of animal physiological signals involves the implant of transducers of physiological activity to electrical signals, that are then processed and acquired. The cables that run these signals from the implants to the acquisition devices carry an inconvenience, as they restrict the capacity of the animal to move freely. In this work, we present a functional prototype of a 4-channel commutator that enables an animal to move around a cage, avoiding the entanglement of the wires. The device was built as an extended student laboratory project at the Physics Department of the University of Buenos Aires, within the framework of a research program that requires the recording of the EMG activity of muscles involved in the production of the Zebra finch song. We show an example of the functioning of the prototype when recording EMG activity (10-50 mV signals) of a freely behaving bird of 12-15 g. weight. Its performance is comparable to that of very expensive, commercial commutators.

Motor Systems

Poster Number 134 / Session III

Mapping temperature induced broken syllables into a dynamical model of birdsong motor pathway

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We study the emergence of complex behaviors in the birdsong motor pathway. Origin of stereotyped motor activities may be the result of precise telencephalic control, or may arise from its interaction with downstream nuclei. Here we present a minimalistic dynamical model that accounts for the diverse respiratory patterns found in the song of birds. Air-sac pressure gestures are obtained as the output of an excitatory-inhibitory non-linear interaction between two neuron populations, driven by an upstream telencephalic instruction. Considering a simple and precise time pattern, we can build a map of frequency and amplitude of this instruction. This picture, called bifurcation diagram, accounts for most of the syllabic morphologies found in canaries (Serinus canaria). It also shows in a comprehensible way, subharmonicity and bifurcations present in the model, that we use as predictions for our cooling experiment. Interestingly, diversity is codified in circuit connectivity, allowing simplicity for the input instruction. Decreasing the temperature of telencephalic nuclei HVC in canaries reduces the frequency of its output activity. We measured song and intra air sac pressure patterns, finding stretching and breaking of syllables, compatible with the predictions of our model.

Motor Systems

Poster Number 135 / Session I

Analysis of the striatal fast-spiking interneurons contribution to the development of L-DOPA-induced dyskinesias.

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L-DOPA-induced dyskinesias (LID) are the more common and incapacitating complication of Parkinson's disease therapy. LID are related to sensitization of a D1R signalling cascade in striatal neurons deprived of dopaminergic innervation and are rarely reversible. Previous studies revealed LID-related morphological alterations in striatal projection neurons but the possible role of the interneurons has only been recently considered. Although the striatal fast-spiking GABAergic interneurons (FSI) constitute only 2% of striatal cells, current studies indicate that they play an important role in the control of striatal excitation-inhibition balance. Our current hypothesis is that chronic administration of L-DOPA induces a diminution of FSI synaptic connectivity to D1 direct-pathway neurons, which results in a higher striatal output and the development of LID. To test it, we will develop an animal model of LID in transgenic mice expressing fluorescent proteins in FSI and D1R striatal neurons. We will study the number of FSI, their dendritic morphology and the connectivity between FSI and D1R striatal projection neurons. Furthermore, we will determine if FSI express the immediately early genes associated with the development of LID by means of immunohistochemistry. We expect that this work will provide innovative knowledge about the changes that take place in the striatum after L-DOPA treatment and its relation with the development of dyskinesias.

Motor Systems

Poster Number 136 / Session II

Motor resonance reflects muscle activity when the goal of the observed action is known

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Passive observation of an action activates the motor system of the observer in a specific manner. This phenomenon, known as motor resonance (MR), can be inferred based on the modulation of the corticospinal excitability (CSE) using transcranial magnetic stimulation. Most previous studies have measured MR at one time point in the action sequence and proposed it reflects the activity of the muscles involved (Fadiga et al, 1995), its goal (Cattaneo et al, 2009), its kinematics (Gangitano et al, 2001), or prediction of future action phases (Urgesi et al, 2010). To further discern among these possibilities we measured the CSE at 4 time points during the observation of grasping actions aimed at two targets. In experiment 1 we determined the time course of movement kinematics and muscle activity during normal execution. First Dorsal Interosseus (FDI) was mostly active when the hand closed to grasp the object, whereas ADM showed no significant temporal modulation. In experiment 2 we filmed videos of the same grasping movements and evaluated the time course of CSE during observation. To allow full prediction we indicated the target of the grasp action before each trial. CSE for the FDI was maximal when the hand closed to grasp the object, whereas the ADM showed no temporal modulation. Our findings suggest that when the goal of the action is known, MR reflects muscle activity of the observed action. We are currently assessing the effect of goal uncertainty on the time course of MR.

Motor Systems

Poster Number 137 / Session III

Analysis of the neural circuits underlying crawling in the leech

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Crawling is a locomotive behavior that the leech undertakes in shallow water and results from alternation between shortening and extension of the body. These movements are achieved by contraction and relaxation of longitudinal and circular muscles. The dorsal excitor 3 (DE-3) motoneuron (MN) and the circular ventral (CV) MN innervate these muscles, respectively. The network underlying crawling is poorly understood. The goal of the present project is to study its structure. We aim at understanding the motor pattern from cellular to network levels. Crawling can be induced in the isolated nerve cord using dopamime. The DE-3 MN activity is recorded extracellularly in the DP nerve and CV MN activity through intracellular recordings. The NS cell is a nonspiking neuron present in each midbody ganglion that is electrically coupled to every MN. Previous results have shown that the NS oscillates in phase with the motor pattern during crawling. Hyperpolarizing the NS neuron membrane potential slows down crawling and decreases the MN firing frequency. This result suggests that the MNs are part of the CPG because the inhibition of these cells not only decreases the firing frequency of the MNs but also slows dawn the rhythm of the motor pattern. We have observed that manipulations of CV membrane potential affect the motor pattern indicating that this MN is part of the CPG of crawling.

Neural Circuit Physiology
Poster Number 138 / Session I

A role for glial connexins in the incorporation of new neurons into the olfactory pathway

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The rodent olfactory epithelium (OE) is capable of sustained neurogenesis, beginning during embryogenesis and continuing throughout adulthood. Formation of neural circuitry involves the ability of a neuron to detect and process cues from glia among other factors. Olfactory ensheathing cells (OECs) are specialized glial cells only present in the afferent olfactory pathway (AOP), which constitute a glial network connected by gap junction (GJ) proteins named connexins (Cxs). OECs promote axon growth both in vitro and in vivo, an effect that is Ca2+-dependent. Given that Ca2+ is a modulator of GJ permeability, we hypothesize that alterations in OECs GJ connectivity affect the way that new neurons incorporate into the AOP. Our aim is to study the incorporation of new olfactory sensory neurons (OSNs) in a transgenic mouse model with reduced expression of OEC connexins during late postnatal development. To do this, we characterize neurogenesis in the OE, we measure the levels of Tyrosine hydroxylase (TH) in olfactory bulb interneurons which are modulated by sensory input, and we quantify the levels of vesicular glutamate transporter (VGLUT2) which is strongly expressed in axon terminals of OSNs. Preliminary results suggest a decrease in the number of TH positive interneurons with no modification in VGLUT2. Our results are compatible with a reduction in OSNs activity, a reduction in OSN number, or both, as a result of the reduction of glial connexins.

Neural Circuit Physiology
Poster Number 139 / Session II

Reduced connectivity of hippocampal-medial prefrontal cortex (mPFC) pathway in a developmental animal model of schizophrenia.

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Ablation of NMDA receptors (NMDAr) in corticolimbic parvalbumin interneurons during early postnatal development results in a schizophrenia-like phenotype after adolescence in mice. This delayed onset reflects an interaction between NMDAr ablation and development during adolescence. Normal refinement of the mPFC continues up to young adulthood and includes synaptic pruning of local and distant inputs, including hippocampal ones. To elucidate the pathophysiological changes leading to schizophrenia-like phenotype in our model we focused our study in the status of functional connectivity between ventral hippocampus (vHP) and mPFC. We positioned a recording electrode in the mPFC to measure local field potentials and a stimulation electrode in the vHP of anesthetized adult control and mutant mice. As a measure of hippocampal-mPFC pathway connectivity we quantified the short latency response evoked by different stimulation intensities. To explore circuit plasticity we used a LTP saturation protocol by applying successive high frequency stimulation (HFS) trains. We observed a decreased connectivity in mutants evidenced by a diminished maximal evoked response. Also, HFS delivered to the vHP induced a significantly reduced LTP response in mutants. We propose that early ablation of NMDAr in interneurons triggers compensatory changes in mPFC circuit leading to exacerbated retraction of excitatory afferents during adolescence.

Neural Circuit Physiology
Poster Number 140 / Session III

Beta oscillations in rodent basal ganglia during active exploration

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Diverse oscillations are present in the Basal Ganglia. 4Hz, Theta (8Hz), Beta (20Hz) and Gamma (30 to 90 Hz) rhythms can be recorded during exploration and are important in the coordination of neuronal circuit dynamics. This picture changes during sleep, where slow oscillations become more prominent (except during REM sleep). In addition, different populations of cells display distinct relationships with each oscillation. However we still don´t know how the relationship between rhythms and cell firing change between active exploration and sleep. In order to explore this I recorded in freely moving animals during active exploration and sleep (REM and no-REM). By means of 4-wire-electrods (tetrodes) I acquired field potential and unit activity in the Striatum, Globus Pallidum and Motor cortex simultaneously. In this exploratory study I focused on beta oscillations since is a prominent rhythm in the Basal Ganglia and activity in this frequency range is increased in Parkinson´s Disease. A better comprehension of these processes will allow us to understand how different oscillations play a role in the coding of cortical information during the performance of various tasks that involve the Basal Ganglia.

Neural Circuit Physiology
Poster Number 141 / Session I

Role of dopamine in corticostriatal postnatal maturation in vivo

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Neurodevelopmental psychiatric disorders as obsessive-compulsive and attention deficit hyperactivity disorder (ADHD) might stem from corticostriatal (CS) malfunction. However, little is known about the functional development of these circuits during adolescence and whether dopamine (DA) pathways are involved in that process. Previously, we found that striatal spontaneous activity (SA) decreases during adolescence but remains elevated in adult mice that had received early DA-depletion (proposed as an ADHD model). Here we show that CS connectivity, in absolute terms, is reduced in adult lesion-mice compared to control mice. Furthermore, the susceptibility to suffer long term depression (LTD) by in vivo high frequency stimulation (HFS) is higher in adult lesion-mice while maximal depression after repeated HFS is the same for all groups. On the other hand, acute D1 and D2 blockade had no effect on CS connectivity or LTD susceptibility, suggesting that DA regulates connectivity and plasticity of CS pathways during adolescence. We propose that the dysregulated level of SA in lesion mice throughout postnatal development acts homeostatically to reduce the cortical input determining a greater capacity of accumulating LTD-like events and lowering CS connectivity in a compensatory manner.

Neural Circuit Physiology
Poster Number 142 / Session II

Ghrelin activates hypophysiotropic CRF neurons through NPY-independent neuronal circuitries.

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Ghrelin is a stomach-derived hormone that regulates appetite and neuroendocrine functions. We have shown that ghrelin activates hypophysiotropic corticotropin-releasing factor (CRF)-producing neurons of the paraventricular nucleus (PVN) and the hypothalamic-pituitary-adrenal (HPA) axis via an indirect mechanism. Since ghrelin activates the neuropeptide Y (NPY) neurons of the arcuate nucleus (ARC), which in turn activates CRF neurons, we tested if intact ARC or NPY signaling are required for ghrelin-induced activation of hypophysiotropic CRF neurons. For this, we administrated ghrelin [2 µg, intra-cerebro-ventricularly (ICV)] to mice with either lesion of the ARC by neonatal treatment with monosodium glutamate (MSG) or previously treated with a combination of specific NPY-1 and NPY-5 receptor antagonists (BIBO3304 and CGP71683 1 µg each, ICV). In MSG mice, we found that ghrelin fully activates c-fos -a marker of cellular activation- in the CRF neurons of the PVN despite the significant reduction of NPY neurons and fibers they have in the ARC and PVN, respectively. In mice with pharmacological blockage of NPY signaling, we found that hypophysiotropic CRF neurons also fully responded to ghrelin. In addition, we found that ghrelin administration directly into the PVN (0.2 µg) also activates both the CRF neurons of the PVN and the HPA axis. Thus, we conclude that ghrelin activates hypophysiotropic CRF neurons through a local neuro-circuitry that is independent of NPY signaling.

Neural Circuit Physiology
Poster Number 143 / Session III

Evidence for an Autonomic Nervous System in an invertebrate, Neohelice granulata.

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In decapod crustaceans intrinsic and extrinsic components that modulate heart rate in fear or flight responses suggest the presence of an autonomic nervous system functionally similar to that of vertebrates. Superimposed to the heart pacemaker, the action of cardio excitatory and inhibitory nerves exert a modulatory effect similar to sympathetic and parasympathetic function. In Neohelice the inhibiton is mainly GABAergic. We recently reported evidence of GABA-like immunoreactivity in the cardiac ganglion region, as well as the partial abolishment of the bradycardia induced by sensory stimulation by the action of the GABAergic antagonist picrotoxin. The goal of this work (which is still in progress) is to examine the excitatory extrinsic pathway that modulates the cardiac response. The immunohystochemical localization of tyrosine hydroxylase has revealed the presence of dopaminergic processes restricted mainly to the Y-shaped ganglionic trunk and forming a network around the large neurons. Additionally, we plan to investigate the neurohormonal action of the biogenic amines 5-HT and dopamine that have been suggested to act on the cardiac ganglion as independent effectors.

Neural Circuit Physiology
Poster Number 144 / Session I

TRANSCRIPTION FACTOR NF-κB AND THE NEURAL MORPHOLOGIC CHANGES ASSOCIATED TO LEARNING AND MEMORY

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Despite that the idea of storing of memories involves morphological modifications in synapses was proposed more than 100 years ago independently by Cajal and Tanzi, it was only recently that solid experimental evidence has confirmed that learning is associated with changes in dendritic spine density. However, little is known about the molecular mechanisms involved in these morphological changes caused by behavioural learning. Besides, the transcription factor NFκB has been involved in memory consolidation and reconsolidation in different paradigms, both in invertebrates and vertebrates. It is also known to trigger the transcription of genes with varied functions, including those potentially involved in morphological plasticity. We tested if NF-κB participates in changes of spine density induced by fear conditioning in hippocampal CA1 pyramidal neurons. We stained mouse hippocampal slices by ballistic delivery of DiI for subsequent confocal imaging of dendritic spines. Our results show that (1)consolidation induces an increase in spine density in both apical and basal dendrites of CA1 pyramidal neurons;(2)the increase in spine density associated to fear conditioning is prevented by intra-hippocampal infusions of NFκB inhibitors; (3)the increase in spine density caused by fear conditioning persists after a reconsolidation protocol; whether the enduring spine increase after reconsolidation also requires NF-kB signalling is still under investigation.

Neural Circuit Physiology
Poster Number 145 / Session II

MMP1 affects circadian structural remodeling of pacemaker neurons in Drosophila.

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Circadian control of behavior depends on the activity of clock neurons in the brain. The small ventral lateral neurons transmit time of day information releasing the neuropeptide pigment dispersing factor (PDF), and likely through the remodeling of the axonal terminals of this circuit. Axonal arborizations show higher complexity during the day and a closed configuration during the night. In this work we demonstrate the relevance of matrix metalloproteinases (MMPs) in the control of this form of plasticity. Flies express only two MMPs, MMP1 and MMP2. Interestingly, adult-specific up-regulation as well as down-regulation of MMP1, but not MMP2, affects not only structural plasticity but also PDF levels at the dorsal terminals. Moreover, normal expression of MMP1 in PDF+ neurons is necessary for the control of circadian behavior. In conclusion, MMP1 is, at least in part, responsible for the daily changes in the axonal arborizations and this structural plasticity affects normal circadian behavior.

Neural Circuit Physiology
Poster Number 146 / Session III

Striatal activity after different degrees of nigrostriatal lesion.

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Electrophysiological studies have provided strong support for the proposition that following dopamine depletion the excitability of the direct and indirect pathways of the basal ganglia moves in opposite directions. Changes in the connectivity of different striatal neurons could be involved in the appearance of clinical manifestation in different stages of dopaminergic depletion. The aim of the present study is to determine the gain of the connectivity between striatal medium spiny neurons from the direct and indirect pathway and their main glutamatergic inputs in different stages of dopaminergic depletion. In order to do that we recorded the responses of striatal neurons to frontal cortex and thalamic intralaminar nuclei electrical stimulation in control, partially and fully dopamine depleted mice. Experiments were performed in transgenic mice that express a fluorescent red protein under the control of the D1 receptor promoter. After being recorded, neurons were labeled with neurobiotin and then revealed with a green fluorescent marker. Prelimary results showing how different stages of dopamine depletion affect striatal neuronal activity in the direct and indirect basal ganglia pathways will be presented

Neural Circuit Physiology
Poster Number 147 / Session I

Functional connectivity between the midline thalamus and dorsal hippocampus in vivo

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The midline thalamus presents mutual connectivity with the hippocampus, with an anatomical selective organization that has not been functionally characterized. The theta rhythm (4-8 Hz) is the hallmark oscillatory pattern of the hippocampus during activated states, whereas sharp-wave ripples take place during deep sleep and immobility. Both rhythms have been proposed to be critical for different aspects of memory formation and spatial navigation. Thus, our objective was to describe the coordinated activity patterns taking place in the midline thalamus and dorsal hippocampus in anesthetized mice. To that end, we performed recordings with two glass electrodes implanted in both the dorsal CA1 region and the midline thalamus. Where thalamic cells were individually recorded and yuxtacellularly labelled for anatomical identification. Our data showed that delta oscillations (2-3 Hz) were the main oscillatory activity present in the midline thalamus, occurring simultaneously with theta oscillations in the hippocampus. Thalamic cells tended to discharge in phase with thalamic delta rhythms, but were not correlated to hippocampal ripple episodes. Our results show that neural circuits in the midline thalamus and dorsal hippocampus are organized around distinct, local oscillatory patterns

Neural Circuit Physiology
Poster Number 148 / Session II

Input processing by adult-born dentate granule cells

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The adult dentate gyrus (DG) generates new granule cells (GCs) that develop and integrate into the preexisting network. Here, we examined whether immature adult-born GCs contribute to information encoding. We worked on acute hippocampal slices obtained from adult mice injected with a retrovirus to express RFP in newborn GCs. Using electrophysiological recordings of postsynaptic responses evoked by activation of the perforant path (PP), we observed that immature GCs required weaker stimuli than mature GCs to be activated, both after single pulses and after 10 Hz trains of stimuli. This suggest that while mature GCs are presumably more selective in their responses, immature GCs could be recruited by different inputs, allowing integrations to occur. To test this hypothesis, we monitored GC activity by loading them with the calcium-sensitive dye OGB-1 AM. Two electrodes were placed to stimulate different and independent PP inputs at various intensities. Under these conditions, the majority of mature GCs responded to only one of the two stimuli, but most immature GCs were recruited by both. Loose patch followed by whole cell recordings reveled that differences in activation profiles were a consequence of differences in the excitation/inhibition balance of afferent inputs. Immature GCs receive slower and weaker somatic inhibition than mature GCs. The observed functions could imply a differential role of mature and immature GCs in processing information arriving to the DG.

Neural Circuit Physiology
Poster Number 149 / Session III

Modulation of glial connectivity in the olfactory pathway

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Neurogenesis in the olfactory epithelium produces olfactory sensory neurons (OSNs) throughout life. Specialized glia, olfactory ensheathing cells (OECs) support the extension of OSN axons along the olfactory nerve up to the central nervous system where they synapse. OECs are gap junction-coupled in a selective manner, which alters their biophysical properties. In addition, OSN activity elicits Ca2+ transients in OECs through glutamate and ATP release and Ca2+ modulates gap junction permeability. Hence, we propose that signals from OSNs modulate OEC gap junction coupling. The aims of this work were to: 1. test whether glutamate and/or ATP modulate OECs connectivity, using electrophysiological techniques in olfactory bulb acute slices and 2. test whether OEC connectivity is affected in a model of degeneration-regeneration of OSNs, analyzing the abundance of the main OEC gap junction protein connexin 43 with inmunohistochemistry. We present preliminary results suggesting that ATP promotes uncoupling of OECs and that the degeneration of OSNs correlates with an upregulation of connexin 43 in the outer layers of the olfactory bulb. Our preliminary results are consistent with the inhibitory effect of ATP on astrocytic gap junction coupling and suggests that the upregulation of connexin 43 observed during OSN degeneration is a compensatory effect after massive ATP release.

Neural Circuit Physiology
Poster Number 150 / Session I

Synaptogenesis of adult-born dentate granule cells onto CA3 pyramidal neurons using optogenetics

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The dentate gyrus generates new dentate granule cells (DGCs) through life. In the adult mouse development and integration of new DGCs takes 6-8 weeks. Whereas afferent synaptogenesis to new DGCs has been extensively characterized, the efferent connectivity remains poorly understood. Previous studies showed that presynaptic terminals onto hilar interneurons are morphologically mature by four weeks, whereas mossy buttons onto CA3 pyramidal neurons remain immature at that neuronal age. These results lead us to hypothesize that immature DGCs initially contact proximal GABAergic interneurons and only later synapse onto distal pyramidal cells. To test this hypothesis we employed retroviral transduction of adult-born DGCs with channelrhodopsin-2 and performed electrophysiological recordings of postsynaptic currents in CA3 pyramidal cells elicited by optical stimulation with a 472 nm laser in acute slices from adult mice. Single pulses or trains of brief blue light stimuli evoked monosynaptic excitatory postsynaptic currents and disynaptic inhibitory postsynaptic currents in 4-6 week old DGCs. Further characterization of the amplitude, kinetics and plasticity of these responses will be performed in order to study the excitation/inhibition balance exerted by developing DGCs in CA3 pyramidal cells.

Neural Circuit Physiology
Poster Number 151 / Session II

Neuronal populations involved in binge eating behaviors

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Binge eating is defined as repeated, discrete and intermittent bouts of consuming unusually large amounts of food. This eating disorder affects 6% of the general population and it is associated to diverse body weight-related pathologies from obesity to anorexia nervosa. The neuronal circuitries and neurotransmitters involved in this behavior are currently unclear. Here, we developed a model of high fat diet (HFD) bingeing in mice and characterized the neuronal systems activated. Using double immunostaining for tyrosine hydroxylase, as a marker of dopaminergic neurons, and c-fos, as a marker of neuronal activation, we found that HFD bingeing activates the meso-limbic pathway. In particular, binge eating recruits dopaminergic neurons of the paranigral and interfascicular subdivisions of the ventral tegmental area. Using a transgenic mouse model that expresses green fluorescent protein in the corticotrophin-releasing factor (CRF)-producing neurons, we found that CRF neurons of the central amygdala are also recruited by HFD bingeing. In contrast, the nucleus accumbens of the ventral striatum failed to show signs of activation in our experimental paradigm. Thus, we conclude that HFD bingeing activates specific dopaminergic and CRF neurons of the reward-related central circuitries.

Neurochemistry and Neuropharmacology
Poster Number 152 / Session III

Evaluation of Memantine effects on the behavioral phenotype of a TDP-43 transgenic model of frontotemporal dementia

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TDP-43 is a major disease protein found in most patients with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), among other neurodegenerative diseases. The NMDA receptor antagonist memantine has been clinically used for the treatment of Alzheimer's disease and other dementias. The purpose of this study was to evaluate if memantine treatment reverses or slows the behavioral impairments displayed by a transgenic mice with conditional overexpression of a cytoplasmically-localized form of human TDP-43. This disease model recapitulates key aspects of FTLD and develops behavioral abnormalities, including altered rotarod performance, spontaneous hyperlocomotion in the open field test and a higher level of disinhibition in the elevated plus maze test. We report here that chronic treatment (1 month) with 30 mg/kg/day memantine, a dose with beneficial effects on several murine models of neurodegenerative diseases, did not alter the expression pattern or distribution of TDP-43. Moreover, memantine treatment did not produce significant changes in the behavioral phenotypes described above. Further studies using different doses and treatment times would be required to elucidate if memantine produces significant behavioral and neuroprotective effects in this animal model.

Neurochemistry and Neuropharmacology
Poster Number 153 / Session I

Notch signaling pathway activation during demyelination-remyelination in rats

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Previously we characterized the cuprizone (CPZ)-demyelination model in rats and demonstrated the promyelinating effect of aTf (Adamo et al 2006). In this work we examined the Notch signaling pathway involvement in the demyelination-remyelination process in CPZ- demyelinated rats. Twenty-one-day-old Wistar rats were fed a 0.6% CPZ diet for 2 weeks. Control animals received a normal diet for the same period of time. Animals were sacrificed 7d before CPZ withdrawal (-7d), the day of CPZ withdrawal (0d), and 7d after (+7d). We evaluated Notch activation through NICD levels and different Notch ligand (Jagged1 and F3/Contactin) expression by WB and immunohistochemical analyses (IHC). We also evaluated the expression of downstream genes Hes1, Hes5 and MAG in SVZ and CC of control and demyelinated animals by Real Time PCR. Results showed Notch pathway activation in response to CPZ-induced demyelination mostly in the SVZ at -7d and 0d. However, during spontaneous remyelination (+7d), we observed an increase in NICD levels in the CC. IHC showed this activation in NG2+ and Nestin+ cells in the SVZ of CPZ animals. An increase in Jagged1 was observed during demyelination in SVZ and CC while, during remyelination (+7d), we found a significant increase in F3/contactin levels in SVZ. These results suggest a participation of the Notch signaling pathway during demyelination-remyelination but its activation seems to be differentially triggered by Jagged1 and F3/contactin ligands.

Neurochemistry and Neuropharmacology
Poster Number 154 / Session II

Activation and potentiation of alpha7 receptors with different number of agonist binding sites

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Neuronal alpha7 nicotinic receptors are homopentameric ligand-gated ion channels, which are emerging as therapeutic targets for treatment of neurological disorders. They are characterized by fast desensitization and brief open-channel lifetime. We studied the relationship between the number of occupied binding sites and alpha7 activation. To generate receptors with different number of functional binding sites we constructed an alpha7 subunit with a mutation that disables the binding site and a reporter mutation that alters conductance, co-expressed mutant and non mutant subunits, and recorded single-channel currents. The current amplitude of each opening reports the number of subunits containing the conductance mutation in the receptor that elicited that opening event, and therefore, the number of functional binding sites. We determined that open-channel lifetime remains constant in receptors with different number of functional binding sites. Lifetime is similarly prolonged by positive allosteric modulators in receptors with 1 or 5 occupied binding sites, indicating that potentiation is independent of the degree of ACh occupancy. Our results reveal a unique feature of alpha7 among other nicotinic receptors: occupancy of only one agonist binding site allows normal activation and potentiation.

Neurochemistry and Neuropharmacology
Poster Number 155 / Session III

Cocaine-induced psychomotor sensitization and microglia activation in nucleus accumbens and striatum

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Repeated administration of cocaine induces psychomotor sensitization, characterized by an augmented locomotor response to a subsequent cocaine challenge and neuronal changes including alterations in the plasticity within the nucleus accumbens (NAc) and striatum (CPu). Microglia cells are resident cells in the brain that become functionally activated in response to injury and diseases. However, it has not been described how the microglia is involved in the psychomotor sensitization and the participation of enkephalinergic system. Male C57B/6J mice were daily treated with cocaine and vehicle for 9 days followed by a cocaine challenge on day 21 of the treatment. The immunohistochemistry was performed in the areas of interest using CD11b and met-ENK antibodies. Cytokines were measured by RT-PCR. In the control treatment microglia cells have small soma and ramified processes. Repeated administration of cocaine induces morphological changes of microglial cells indicative of cell activation and also increased production of pro-inflammatory cytokines such as TNF-α. We observed co-localization of met-ENK with CD11b in microglia. These preliminary results could be a key to better understanding the role of immunological signaling system in drugs addiction which might become in a new therapeutic target.

Neurochemistry and Neuropharmacology
Poster Number 156 / Session I

Oxygen free radicals mediate potentiation of the GABAρ1 receptor function by H2O2.

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Reactive oxygen species (ROS), such as hydrogen peroxide (H2O2), superoxide anion (O2-.) and hydroxyl radical (OH.), have been implicated as intracellular regulators of neuronal activity and diffusible messengers for neuron-glia signaling. Increased production of ROS produces oxidative stress and damage to the central nervous system, as seen in normal aging and neurodegenerative disorders. Diverse neurotransmission systems are modulated by ROS, including the adrenergic, dopaminergic, serotonergic and GABAergic. We previously demonstrated that H2O2 potentiates homomeric ρ1 GABA receptor (GABAρ1R) function trough the intracellular Cys-364. Now we analyzed the mechanism underlying this modulation. H2O2 could directly oxidize Cys-364 or could act indirectly by the formation of the free radical OH. in the presence of iron (Fenton reaction). GABAρ1R were expressed in Xenopus laevis oocytes and GABA-evoked chloride currents electrophysiologically recorded in the presence of H2O2 and modulators of the OH. concentration. Lipoic acid (free radicals scavenger) or deferoxamine (iron chelator) prevented H2O2 potentiation whereas pre-incubation with FeSO4 enhanced it. These results suggest that oxygen free radicals mediate the potentiation of the GABAρ1R function by H2O2.

Neurochemistry and Neuropharmacology
Poster Number 157 / Session II

Transgenic C. elegans as a model of congenital myasthenic syndromes

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The free living nematode Caenorhabditis elegans is a model for the study of human neurological diseases and drug testing. Our goal is to establish C. elegans as a model of slow-channel congenital myasthenic syndromes, which are originated by gain-of-function mutations in nicotinic receptor subunits. We introduced a mutation in the 9' position of the M2 domain of UNC-38 (V9'S), an essential alpha-type subunit of muscle levamisole-sensitive nicotinic receptor (L-AChR), and generated transgenic worms that express the mutant subunit in muscle. Single-channel recordings from isolated muscle cells show a dramatic increase (about 10-fold) in the open duration of L-AChR channels. Single openings appear, in contrast to wild-type channels, grouped into long activation periods. Macroscopic currents are 3-fold smaller than wild-type currents and do not decay in the presence of ACh. The functional changes of L-AChR in the mutant worm mimic those observed in vertebrate AChRs carrying the equivalent mutation. Our results reveal a high degree of conservation of functional roles of amino acids between C. elegans and human AChRs, thus opening doors for studying other gain-of-function mutations associated to slow-channel syndromes.

Neurochemistry and Neuropharmacology
Poster Number 158 / Session III

Understanding why partial agonists of serotonin receptors do not produce maximal responses

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Partial agonists activate receptors with partial efficacy relative to full agonists. Our goal is to understand the reasons for which two classical partial agonists of 5HT3A receptors, 2-Me-5HT and tryptamine, produce submaximal responses. To this end, we recorded single channels of the high conductance form of the 5-HT3A receptor activated by 5-HT and partial agonists. For all agonists, activation appears as openings in quick succession grouped in clusters with high open probability (Popen>0.9). All recordings show the presence of three different open states. The longest duration state is 6.5- and 3.5-fold briefer for 2-Me-5HT and tryptamine, respectively, than for 5-HT. The duration of this open state decreases with agonist concentration due to open channel blockade. For 2-Me-5HT, the forward blocking rate is 10-fold higher than for tryptamine or 5-HT, and blockade leads to a reduction of Popen from 0.95 to 0.30 (from 1 to 50 μM). Interpreting the data on the basis of kinetic schemes shows that 2-Me-5HT does not produce maximal response mainly because it acts as a potent channel blocker. In contrast, tryptamine is a genuine partial agonist and its low efficacy is mainly due to a slow transition from the fully-liganded closed state to a pre-open state. After reaching this latter state, activation proceeds similarly as in the presence of 5-HT.

Neurochemistry and Neuropharmacology
Poster Number 159 / Session I

Role of Wnt/b-catenin signaling pathway in the development of cocaine induced sensitization

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Wnt factors are cysteine rich secreted proteins that interact with their receptors: Frizzled, Ryk, and Ror. As a result of the interaction, Dishevelled (DVL) is activated, and consequently, one of three pathways: Wnt/b-catenin, Planar Cell Polarity, or Wnt/calcium pathways. Wnt signaling pathways are essential for development of the mammalian brain. However little is known regarding its role in adulthood. Our main goal is to elucidate if the Wnt/b-catenin signaling pathway participates in cocaine sensitization. Then, adult male Wistar rats received cocaine injections daily for a week and motor activity was recorded on Day 1 and Day 7. At different times after cocaine injection on Day 7 animals were sacrificed, and brains areas were dissected to study expression levels of b-catenin in total homogenates as well as cellular subfractions. Our data showed changes in response to daily cocaine injections only in Prefrontal Cortex (PFC) and no changes were found in Nucleus Accumbens, while Dorsal Striatum showed changes at both acute and daily cocaine injections. Furthermore, ongoing studies are evaluating mRNA levels of Wnt by RT-PCR. So far our data suggests that b-catenin in PFC is involved in the development of cocaine induced sensitization.

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Expression of Stress-Induced Sensitization to Cocaine is Associated to Changes in ABPs and GluR1 in the Nucleus Accumbens

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Behavioral sensitization is an example of experience-dependent plasticity, induced by drug or stress, which has been suggested to involve plasticity at glutamatergic synapses and and there is evidence for a common mechanism triggered by stress and drugs at excitatory synapses on midbrain dopamine neurons. These experiments evaluated how the expression of restraint stress-induced sensitization to cocaine (15 mg/kg i.p.) is associated to alterations in actin binding proteins (ABPs) and the surface expression of GluR1 in nucleus accumbens (NAc). Our experiments revealed a decrease in p-cofilin and p-cortactin, and an increase in GluR1, in the stress plus cocaine group as was previously shown after cocaine (30 mg/kg). The stress-induced sensitization to cocaine was prevented by either latrunculin A or CNQX. Interestingly, latrunculin A also reversed the stress/cocaine-induced increase in GluR1, indicating a potential role for actin cytoskeleton in the increased AMPAR. This study shows that a history of repeated stress alters the ability of a subsequent cocaine injection to modulate dendritic spine morphology, actin dynamics and AMPAR expression in the NAc. Furthermore, by regulating AMPAR expression, elevated actin cycling contributes to the expression of cross-sensitization.

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THE DOPAMINERGIC ANTAGONIST HALOPERIDOL ALTERS PUPS VS MALE PREFRENCE (AND SEXUAL BEHAVIOR) OF POSTPARTUM ESTROUS RATS

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During the postpartum estrus (PPE) rats are sexual and maternal motivated, however in a pup-male choice test, they prefer pups and make more effort to gain access to them. As the dopaminergic (Da) system has been mainly implied in the activationally aspects of motivated behaviors, we postulate that the reduction of the Da transmission decreases the effort to obtain pups of PPE dams, without affecting their preference. To test this hypothesis, PPE females were treated with Da antagonist haloperidol (HAL: 0.0,0.025, 0.050 mg/kg, -60 min) and tested in a Y-model with three choice chambers: pups and male (reinforcing stimuli) and non-receptive female (neutral stimulus). Afterwards, a sexual behavior test was performed to determine the effect of these doses of HAL on PPE females´ sexual activity. As expected, both doses of HAL reduced the effort made by mothers to get the pups. The total time in the three chambers did not change, however HAL modified females` preference: saline- 6/9 prefer pups and 1/9 male; 0.025 HAL- 3/10 prefer pups and 4/10 male; and 0.05 HAL- 1/8 prefer pups and 0/8 male. Both doses increased the duration of dams´ lordosis, while only the highest reduced sexual solicitations. Together, these results suggest that a high dose of this Da antagonist strongly down regulates both motivations, but the low dose differentially affects sexual and maternal motivations or, alternative, enables the expression of sexual motivation by reducing the effort to obtain the pups.

Neurochemistry and Neuropharmacology

Poster Number 162 / Session I

Involvement of serotonin in cognitive flexibility in rats

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We have previously described the role of serotonin (5-HT) in the acquisition of an operant conditioning task. Here we studied the role of 5-HT in the reversal of this reward-dependent learning. First, animals were trained in an operant conditioning task, followed by several extinction sessions. We found that Fluoxetine administration (a 5-HT reuptake inhibitor) improved the extinction of the rule, i.e., the animals needed fewer sessions to achieve a low number of incorrect responses. Instead, animals treated with Tianeptine (a 5-HT reuptake enhancer) had the opposite effect; rats had a higher number of incorrect responses even after several sessions of extinction. Then, we assayed the effect of Buspirone (a 5-HT1A receptor agonist). Buspirone did not have an overall effect on the extinction of the task, nevertheless, a slightly higher number of incorrect responses was observed in the last sessions. The 5-HT2A receptor antagonist Risperidone exerted a drastic effect on reversal learning; animals achieved a complete extinction after a few sessions. Finally, the 5-HT3 antagonist Ondansetron also improved the ability of the rats to learn the new rule faster than the controls. Taking into account our prior results, these data suggest that 5-HT plays an important role in cognitive flexibility, acting as a dual codifier of the reward and the lack of the same.

Neurochemistry and Neuropharmacology
Poster Number 163 / Session II

In vitro evaluation of neuroprotective effects of colombian propolis

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Oxidative Stress is the product of excessive formation of oxidizing species and a decrease in the efficiency of endogenous antioxidant systems. This condition has aroused great interest as it could be related to the etiopathogenesis of Neurodegenerative Diseases associated with aging, like Alzheimer and Parkinson. The development of antioxidant therapies for treating these neuropathies, has allowed the identification of natural substances, like propolis. It has been suggested that the high antioxidant activity of propolis is given by the concentration of polyphenol like flavonoid, determined by the botanical and geographical origin of each sample of propolis. Botanical diversity that characterizes Colombia drives our study to evaluate the antioxidant capacity of colombians propolis, in two different models of neurodegeneration in vitro: H2O2 and KCl. Propolis were evaluated from 3 different regions, including a control sample of Brazilian Green Propolis. The viability data obtained with MTT test showed that none of the Colombian samples presented protective effect in the human neuroblastoma cell line SHSY-5Y exposed to H2O2 or KCl ($p \geq 0.05$). Data obtained from the LDH assay supports the previous data, also showing no protection from Green Propolis of Brazil when treated with KCl ($p \geq 0.05$). In conclusion, propolis included in our study do not exhibit a significant antioxidant capacity against the cytotoxic effects of H2O2 and KCl.

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Changes in the Glutamate homeostasis in Nucleus Accumbens Core underlies the stress-induced sensitization to cocaine: implicance of GLT-1

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Sensitization is associated with neuroplasticity in the dopaminergic (DA) and glutamatergic (GLU) mesocorticolimbic systems. It is well know that withdrawal (2-3 weeks) from chronic cocaine, induced changes in synaptic glutamate transmission and glutamate transporter-1 (GLT-1) expression in the nucleus accumbens (NAc). The aim of our study was to evaluate the influence of restraint stress and its interaction with cocaine (15 mg/kgi.p.) on the levels of GLT-1 and the relationship with the extracellular GLU in NAc. Male Wistar rats (250-350 g) were restrained for two hours, while control animals were left undisturbed in their cages. Twenty-one days after this stress episode, animals were assigned to one of the following experiments: I) Western blot: GLT-1 expression in gliosomes from NAc Core after i.p. injection of saline or cocaine (15 mg/kg). II) Microdialysis: GLU release was measured by HPLC in NAc Core and NAc Shell in response to saline and cocaine (15 mg/kg i.p.); and basal GLU levels were measured by no-net-flux technique. Our results demonstrate that the alterations in basal and extracellular GLU appeared consequential from GLT-1 decreased expression in Core in the stressed group.

Neurochemistry and Neuropharmacology

Poster Number 165 / Session I

Modafinil treatment prevents methamphetamine-triggered effects on pro-apoptotic BAX and anti-apoptotic Bcl-2 protein expression in mice striatum

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Methamphetamine (METH) intake can cause neurotoxic damage in human users and animals. METH toxic effects include terminal degeneration and pro-apoptotic effects. Our group had previously demonstrated that Modafinil (MOD), a psychostimulant drug used to treat sleep disorders, could protect against METH-induced striatal toxicity. To further evaluate the role of MOD in neuroprotection, we first studied the temporal profile of METH-induced toxicity in the striatum with the Amino-Cupric-Silver technique. Female C57BL/6 mice, treated with a METH "binge" protocol (4x5mg/kg, ip, 2 hs apart), showed the highest degree of terminal degeneration at 16 and at 24 hs in comparison to vehicle-treated controls, therefore we decided to evaluate possible protective effects of MOD at 16 hs post METH. Mice were treated with the METH binge protocol, MOD (2x90mg/kg, ip), or with the combination of MOD+METH (2x90mg/kg, ip, 1h before the 1st and 4th METH injections). The protein expression of the pro-apoptotic BAX and the anti-apoptotic Bcl-2 was analyzed in mice striata. We found a significant increase in BAX and a decrease in Bcl2 expression in METH-treated mice. Neither MOD nor the MOD+METH combination groups showed significant changes in comparison to vehicle-treated subjects. These results indicate that MOD might protect against METH toxicity, at least in part, by interfering with METH-induced changes in pro- and anti-apoptotic signals.

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Poster Number 166 / Session II

GABA-induced regulation of allosteric interactions between GABA and benzodiazepine sites in rat neocortical neurons

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We have previously showed that a brief exposure of rat neocortical neurons to GABA (t1/2 3.2 min) produces hours later (t1/2 12 h) an uncoupling of the interaction between GABA and benzodiazepine sites, without changes in GABAA receptor number. Since the strength of allosteric coupling depends on the α subunit subtype present in the GABAA receptor (rank order: α3 > α1/5), the aim of this work was to determine whether uncoupling is produced by alterations in the receptor subunit combination. To this end, neocortical cultures were incubated with GABA for 10 min and cells were collected 48 h later. Receptors were immunoprecipitated with an antibody anti- γ2 subunits, that are present in most of the receptors, and analyzed by western blot. We observed a decrease in α3γ2 and an increase in α5γ2 receptor number. The number of α1γ2 receptors remained constant. We next performed a biotinylation assay followed by western blot to measure the cell surface expression of α3 and α5 subunits. GABA induced a reduction in plasma membrane levels of α3 but no significant change in surface expression of α5. These results suggest that GABA-induced uncoupling involves a change in the subunit composition of GABAA receptors, resulting in a reduced coupling between GABA and benzodiazepine binding sites.

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GABA receptors of muscle Caenorhabditis elegans as targets of anthelmintic agents

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Gamma-aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in vertebrates and invertebrates. GABA receptors are targets of anxiolytic and antiepileptic drugs as well as of insecticides and anthelmintics. In nematodes, GABARs are present in the muscle and the appropriate balance of acetylcholine and GABA signaling is required for coordinated contraction and movement. We studied muscle GABARs from C. elegans to characterize and evaluate at both the molecular and behavioral levels the mode of action of GABAergic agonists and anthelmintics. Single-channel currents of ~2.5 pA from GABARs activated by GABA, muscimol and piperazine can be detected from cell-attached patches in muscle cells. Macroscopic current recordings show full desensitization of GABARs in the presence of the three agonists and indicate that piperazine is less efficacious than GABA. Behavioral assays show that piperazine produces flaccid paralysis and that its effect is potentiated by ivermectin, a positive allosteric modulator of GABARs. Our results also show differential sensitivity to these drugs between adult and larval stages. The lack of GABARs in vertebrate muscle highlights the importance of their characterization in nematodes, not only from an evolutionary point of view but also for the development of more selective anthelmintic therapies.

Neurochemistry and Neuropharmacology
Poster Number 168 / Session I

Potential Central Nervous System effects of the synthetic flavonoid 3,3-dibromoflavanone

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The pharmacotherapy for mental disorders and the treatment of pain is an active area of investigation. We have demonstrated the significance of flavonoids on the central nervous system (CNS) and classified them in: 1) natural or synthetic substituted flavones with affinity for the benzodiazepine binding site of the GABAA receptor with anxiolytic action; 2) glycosilated flavonoids with sedative, hypnotic and antinociceptive properties in vivo presumably acting via an opioid mechanism of action. From our library of natural and synthetic flavonoid derivatives, 3,3-dibromoflavanone (DBF) evidenced affinity for the mu-opioid receptor. We have synthesized and studied its effects on the CNS. DBF showed no sedative, anxiolytic, antidepressant or motor incoordination effects. It showed antinociceptive activity in which adrenoceptors, 5-HT2, δ and κ opioid receptors are not involved. Naltrexone, a nonselective opioid receptors antagonist, totally blocked DBF antinociception. DBF inhibited the specific binding of [3H]DAMGO (Ki: 0.85 ± 0.26 μM) in mice cerebral membranes. These results will contribute to develop new drugs with CNS effects from flavanone structures.

Neurochemistry and Neuropharmacology
Poster Number 169 / Session II

Pharmacological analysis of Dopamine neurotransmission in hyperactive mice lacking p35

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Background: Previous research in our lab showed that a genetically modified mice lacking p35 (the specific activator of cyclin dependent kinase 5) exhibit spontaneous hyperactivity, that is ameliorated by the administration of psychostimulants drugs (Krapacher et al. 2010. J Neurochem, 114, 203-214). This hyperactivity and its paradoxical response to psychostimulants are related with an impairment in dopaminergic neurotransmission and represent a core characteristic of ADHD animals models. Objectives: Analyze the functional state of dopaminergic neurotransmission in p35 KO mice through the use of a series of drugs that interfere with the normal function of dopamine receptors. To study the status of the D1 receptor(r) we use the agonist of D1 SKF81297 (5mg/kg ip) and the antagonist SCH23390 (0,05mg/kg ip). In the other hand, to explore the integrity of D2-mediated neurotransmission we administrated the agonist quimpirole (0,5mg/kg ip) and two different doses of the antagonist haloperidol (0,03mg/kg or 0,1mg/kg ip) in wild type (WT) and p35 KO mice. Results: the pharmacological manipulations had the same effect in both animals, producing a reduction of the locomotor activity (by D1r antagonism and D2r agonism/antagonism) or increasing the locomotor activity (D1r agonism). These results indicate that dopamine receptors are functional in p35 KO mice, suggesting that the hyperlocomotor behavior of these mice is not a direct consequence of dopaminergic receptor alteration.

Neurochemistry and Neuropharmacology
Poster Number 170 / Session III

Evolutionary changes in the pharmacology of the nicotinic α9α10 receptor

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The α9α10 nicotinic acetylcholine receptor (nAChR) mediates efferent inhibition of vertebrate hair cells. A phylogenetic analysis showed signatures of positive selection exclusively in the α10 subunit within the mammalian lineage (Franchini& Elgoyhen, 2006). Here, we assayed the effects of these non-synonymous substitutions by comparing the pharmacology of recombinant chicken and rat receptors. We found that the effects of the agonists choline and DMPP and the antagonist serotonin on chicken receptors differ from those on rat α9α10 receptors and resemble those on rat α9. Above all, choline showed higher efficacy on chicken α9α10 receptors (88±8% max response to ACh, n=4) compared to rat α9α10 receptors (34±4% max response to ACh, n=4). Moreover, in a Ratα9Chickα10 hybrid receptor, responses to choline were 88±7% (n=2) of the maximal response to ACh, resembling chicken receptors and strongly suggesting that the sites involved have been altered in mammalian α10 subunits. We conclude that the aminoacid changes that accumulated on mammalian α10 subunits resulted in the pharmacological differences observed. Most importantly, we propose that the efficacy of choline (the main synaptic metabolite of ACh) to elicit a response may lay behind the selection pressure on mammalian α10 subunits.

Neurochemistry and Neuropharmacology
Poster Number 171 / Session I

Involvement of the enkephalinergic system in the dopamine sensitization to cocaine in the nucleus accumbens.

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Endogenous opioid peptides, mainly enkephalin, are largely distributed in the mesolimbic system. However, their contribution to cocaine - induced sensitization on behavioral and neurochemical parameters has been poorly studied. Male C57B/6J wild type (WT) and preproenkephalin knockout (KO Penk) mice were daily treated with cocaine (15mg/Kg i.p.) and vehicle for 9 days. On day 21 of the treatment the following experiments were done: I) Microdialysis: dopamine extracellular levels were measured by HPLC in nucleus accumbens in response to saline and cocaine challenge (7,5mg/Kg). II) Immunohistochemistry: met enkephalin levels were determined in nucleus accumbens and striatum in response to saline and cocaine challenge. Our results demonstrated that Penk KO mice did not show sensitization to the neurochemical effects induced by cocaine, as it was shown in wild type mice treated chronically with the drug. Despite the fact that dopamine levels in response to an acute dose of cocaine was similar in both genotypes. Concurrently, wild type mice evidenced an increase in met-enkephalin levels induced by cocaine treatment in nucleus accumbens and striatum. These results indicate that enkephalinergic system is strongly involved in the dopamine sensitization to cocaine in the nucleus accumbens from animals chronically treated with cocaine.

Neurochemistry and Neuropharmacology
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N-butyl-1,2,3-oxathiazolidine-4-one-2,2-dioxide, a new anticonvulsant compound with antioxidant properties

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Epilepsy is recognized as one of the most common and serious neurological disorder affecting 1-2% of the world's population. Among various factors supposed to play role in epilepsy, oxidative stress and reactive species (ROS) in seizure disorders have recently emerged. The most important effect of free radicals is lipid peroxidation (LP), which causes disruption of cell membrane thereby leading to their destruction. An increased of free radicals also decreased glutathione (GSH) concentration in the epileptic focus. We have synthesized a bioisoster of trimethadione (a classical anticonvulsant), N-butyl-1,2,3-oxathiazolidine-4-one-2,2-dioxide, which showed anticonvulsant properties in MES and PTZ test. This new anticonvulsant with ED50 of 18 mg/kg (scPTZ), has been tested for its antioxidant properties. N-butyl-1,2,3-oxathiazolidine-4-one-2,2-dioxide administrated before PTZ treatment countered the effects of PTZ and protected brain from oxidative stress by decreasing the LP and restoring the GSH content.

Neurochemistry and Neuropharmacology
Poster Number 173 / Session III

An heterobifunctional probe binds an allosteric site on the nicotínic acetylcholine receptor

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The probe (AC4-ASA) was developed as a tool for the study of cholinergic receptor binding sites. Acetylcholine was derivatized at its alkyl end and, through a short spacer, with a photoactivatable aryl-azide group susceptible to radioiodination. The probe was able to interact specifically with the muscle nicotinic receptor and has a considerable selectivity for its α/δ binding site. This ligand showed the capability of modyfing the affininty of (-)-[3H]-nicotine for the muscle-type nicotinic receptor. Competition experiments between AC4-ASA and (-)-[3H]-nicotine revealed that the ligand could perform its modulating activity through, at least, one new allosteric binding site, different from the typical orthosteric binding sites. With the aim of delineating this site, the Torpedo californica receptor was modified with the ligand and submitted to SDS-PAGE. All subunits were digested with trypsin and peptide mixtures analyzed by MALDI-TOF-TOF mass spectrometry. Spectra from the alpha and delta subunits allowed us to find several m/z signals, absent in the non-modified receptor subunits. After a detailed analysis of such signals we were able to postulate that they correspond to determinants of ligand binding sites. Moreover, most of them are not involved in the orthosteric sites thus suggesting that could be participating in the allosteric one.

Neurochemistry and Neuropharmacology
Poster Number 174 / Session I

GABAA RECEPTORS MEDIATE ANXIETY-LIKE BEHAVIOR INDUCED BY GHRELIN IN NEONATAL CHICK FOREBRAIN

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Ghrelin is a 28 aa peptide with homology between species and has an anxiogenic action in rodents and birds. The GABAergic system is modulated by stressful events that modulate the synaptic transmission and strength. In chicks, has been identified a high density of GABA A receptor (GABAAR) in the intermediate medial hyperstriatum ventrale (IMHV), a telencephalic area that is crucially involved in the process of imprinting. In the present study, we evaluated the involvement of GABAAR in the anxiogenic-like effect of ghrelin. In the first experiment, bilateral injections of ghrelin into the IMHV significantly increased the latency to ambulate in an Open Field test in a dose-dependent manner (15-900pmol) compared to saline control, indicating an anxiogenic action. In the second experiment, the ip injection of 0.036 and 0.36 mg/kg of bicuculline (antagonist) blocked the response induced by ghrelin (30pmol) on anxiety-like behavior in the Open Field test. These results demonstrate for the first time the participation of GABAAR in anxiogenic action of ghrelin. In addition, the IMHV, an area strongly involved in processing memory, also plays a central role in the expression of stress-related behaviors.

Neurochemistry and Neuropharmacology
Poster Number 175 / Session II

Partial blockade of cocaine induced sensitization by activation of Wnt signaling pathway

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Wnt factors are cysteine rich secreted proteins that interact with their receptors: Frizzled, Ryk, and Ror. As a result of the interaction, Dishevelled (DVL) is activated, and consequently, one of three pathways: Wnt/b-catenin, Planar Cell Polarity, or Wnt/calcium pathways. Wnt signaling pathways are essential for development of the mammalian brain. However little is known regarding its role in adulthood. Preliminary results from our lab showed a decrease of b-catenin in Prefrontal Cortex after cocaine induced sensitization. It has been shown that Lithium Chloride (LiCl) increases b-catenin levels. Therefore, in order to elucidate if the changes in b-catenin are related to behavioral sensitization, we administered LiCl i.p. or into PFC before each cocaine injection during the treatment. Then we compared the behavioral response between first and last cocaine injection. Animals were sacrificed 24hs after last injection and brain areas were dissected. So far our results showed that systemic as well as intra-PFC LiCl injections partially blocked cocaine induced sensitization. Ongoing studies are aimed to evaluate if LiCl pretreatment also modifies b-catenin levels.

Neurochemistry and Neuropharmacology
Poster Number 176 / Session III

Impairment in hippocampal GABAA receptors binding after moderate noise exposure

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Moderate noise-induced damage on the hippocampus (HC) may result from the disruption of the balance between excitatory and inhibitory neurotransmission (NT). The aim of the present work was to investigate if the exposure of developing rats to moderate noise levels induced changes in HC GABA binding that could underlie the previously observed behavioral and histological alterations. Male Wistar rats of 15 days were exposed to white noise (95-97 dB, 2h) for one day or for 15 consecutive days. Hippocampal GABAA binding was measured at 15 and 30 days. Results show that noise induced a significant decrease in HC GABA Bmax at 2 h after the first exposure (56%, $p < 0.0001$), without changes in Kd. In contrast, after 15 days, one day exposure induced an increase in Bmax (175%, $p < 0.001$), while no changes were observed in HC GABA Bmax after multiple exposures. These results suggest that noise might induce an imbalance in hippocampal aminoacidergic NT that could be responsible for the tissue damage. Furthermore, GABAA receptor downregulation could be compensated by a subsequent upregulation. These data suggest that developing GABAA receptors might adapt to a new inhibitory status. Therefore, it might be hypothesized that impaired inhibitory synaptic transmission could contribute to trigger cell death. Since GABA receptors are differentially affected, these results could underlie the changes in anxiety previously reported.

Neurochemistry and Neuropharmacology
Poster Number 177 / Session I

Exogenous GM1 ganglioside increases the rewarding properties of cocaine and the expression of BDNF in the nucleus accumbens

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We recently reported that GM1 pretreatment enhances the rewarding properties of cocaine, evidenced by a reduction of the dose of cocaine necessary to induce conditioned place preference (CPP), as well as by the number of sessions necessary for conditioning. To clarify the mechanism of such an effect, different pharmacokinetic parameters of cocaine, and its inhibitory effect on the dopamine transporter were evaluated. None of these parameters was modified by GM1 pretreatment, but it modified the brain cocaine disposition. In order to explain the effect of GM1 on the rewarding properties of cocaine, in the present study we examined whether exogenous administration of GM1 induces the expression of BDNF in the nucleus accumbens (NAc). Thus, adult male rats were submitted to 3 conditioning sessions with cocaine (10 mg/kg), and following the CPP test were sacrificed, the NAc was dissected and prepared for BDNF determination. Only GM1 pretreated rats (30 mg/kg) showed an increase of the rewarding properties of cocaine, an effect correlated with a significant increase of BDNF levels in the NAc. These preliminary results, suggest that GM1 may promote the increase effects of BDNF, by activating mechanisms of associative learning that underlie the conditioned responses to cocaine.

Neuroendocrinology and Neuroimmunology

Poster Number 178 / Session II

INVOLVEMENT OF KININ B2 RECEPTORS IN THE DEVELOPMENT OF THE PILOCARPINE-INDUCED EPILEPSY IN FEMALE RATS

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Aims: Kinins, a class of polypeptides represented by bradykinin, kallidin and their metabolites, acting via B1 and B2 receptors. Several studies indicate that in peripheral tissues, estrogen regulates the expression of B2 receptor. Accordingly, the present work aimed to investigate the expression of kinin B2 receptor in female rats, submitted to the pilocarpine model epilepsy. Methods - Results: The animals were divided in four groups: OVX + SE (status epilepticus ovariectomized female rats); SE: intact female rats that presented SE; OVX ovariectomized female rats that received saline instead pilocarpine; SAL intact female rats that received saline. The results showed a decrease of immunoreactivity of kinin B2 receptor in the hippocampal formation during the acute and silent in SE group when compared to SAL group. In contrast, the immunoreactivity in OVX + SE group was increased during the acute and silent periods when compared with OVX group. The Western Blotting showed an increased expression of kinin B2 receptor in OVX +SE group during the acute ($p=0.0034$) and silent periods ($p=0.0277$), when compared with its proper controls (OVX). In addition, a decreased expression in SE group during the acute ($p=0.0039$) and silent periods ($p=0.0121$) were found, when compared with its proper control. Conclusion: This study showed that the expression of kinin B2 receptor is modified in female rats during epileptogenesis and modulated by steroid hormones.

Neuroendocrinology and Neuroimmunology

Poster Number 179 / Session III

Characterization of the relationship between NEI, TH and GAD-67 in hypothalamic brain areas of hypo- and hyperthyroid adult male rats

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Neuropeptide glutamic-acid-isoleucine amide (NEI) is a 13 aminoacid peptide derived from pp-MCH. Hypo- and hyperthyroidism modify NEI concentration in discrete brain areas of male and female rats [Ayala C et al. 2011]. The aim of the present study is to characterize the relationship between NEI-ir cells and fibers with tyrosine hidroxilase (TH) and acid-glutamic-descarboxilase-67 (GAD-67) in hypothalamic brain areas of hypo- and hyperthyroid adult male rats by means of immunofluorescence and confocal microscopy. Animals were divided into control, hypoT and hyperT (n=3 per group) and perfused 21 days after starting the treatment. The areas under study are the incerto-hypothalamic area (IHy), the peduncular part of the lateral hypothalamus (PLH) and the perifornix (PeF). Images are processed with Image J software. In the IHy at – 1.92 mm distance from Bregma, a 3D reconstruction was used to analyze the relationship between NEI and TH somas and dendritic tree. The optical density, cell area, the number of terminals and contact sites are quantified for each brain area and treatment. Differences among experimental groups are expected to be found according to preliminary observations. Proyecto ANPCYT-PICT 23529-2005, SECyT-UNC.

Neuroendocrinology and Neuroimmunology

Poster Number 180 / Session I

PRESINAPTIC DYSFUNCTION IN DIFFERENT BRAIN AREAS OF RATS WITH EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE).

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EAE is a model that mimics many of the clinical and pathological features of multiple sclerosis (MS). While MS and EAE research has been mostly focused on spinal cord inflammation/demyelination, the extent and implications of gray matter damage are still not fully understood. Herein we show that Ca2+-dependent glutamate release from isolated synaptosomes is specifically impaired in frontal cortex and striatum from rats with EAE, with no changes in total glutamate content. Synapsin I is necessary for synaptic vesicle mobilization to the active zone as well as for vesicle recycling and anchoring to the actin cytoskeleton. The first event is regulated by CaMKII phosphorylation of P-sites 1 to 3 and the latter is triggered by Erk1/2 (MAPK) phosphorylation of P-sites 4 and 5. In synaptosomes from EAE rats, depolarization-induced phosphorylation on P-site 3 of Synapsin I is reduced whereas Erk1/2 autophosphorylation is increased. All these changes rapidly reverse when the animals begin to recover from the clinical signs of the disease. These data indicate that presynaptic machinery is affected in EAE, unraveling in part the mechanism of neural dysfunction. Since this occurs in brain areas related to motor control and learning it might contribute to the disease progress.

Neuroendocrinology and Neuroimmunology

Poster Number 181 / Session II

Maternal Separation and Chronic Variable Stress during adulthood: Implications for Glucocorticoid Receptors Expression in Limbic areas related to Anxiety and treatment with tricyclic antidepressant Amitriptyline

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During early life, environment promotes different pathways of expression of molecules in the brain which will determine diverging responses to stress in adulthood. This involves two types of receptors for corticosteroid: mineralocorticoid (MR) and glucocorticoid (GR) receptors. The aim of this work was evaluate changes after chronic variable stress (CVS) in rats previously early maternally separated (MS). We measured anxiety-like behavior and immunoreactivity (IR) of GR and MR in Amygdala and Septum, areas related to the control that behavior. During the CVS protocol in adulthood, animals were treated with Amitriptyline (AMI) (10 mg/Kg i.p.). Concerning GR, CVS evoked a slight rise in GR-IR in non-MS rats which was effectively prevented by AMI in the Medial Amigdaloid Nucleus (MeAm). Regarding MR, MS evoked less MR neurons in Central Amigdaloid Nucleus which was prevented by AMI and more MR-IR in Septohippocampal nucleus with no effect of AMI or CVS. The combination of MS and CVS and AMI produced diminution of MR-IR in Central Amygdala. Similar effect was observed in MeAm. No effect of the combination on Septum. Regarding anxiety-like behavior, CVS evoked a marked tendency to increase anxiety and AMI exerted an anxiolytic effect on these animals. When CVS was combined with MS, the anxiogenic effect was potentiated and it was not reversed by the antidepressant because the combination also evoked less motility activity.

Neuroendocrinology and Neuroimmunology
Poster Number 182 / Session III

Selective Denervation of Noradrenergic end-terminals in the Medial Preoptic Area by DSP-4: A Method to study the role of Locus Coeruleus in the Reproductive Function

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In female rats, the release of LH depends on the activity of GnRH neurons in the medial preoptic area (MPOA), which is modulated by neurotransmitters that respond to changes on sex steroids levels. Among them, noradrenergic neurotransmission from brainstem nuclei in the MPOA have shown to be decisive. We verified the efficacy of the neurotoxin DSP-4 as a method of selective denervation of noradrenergic terminals from LC in MPOA by measuring noradrenaline (NA) and its metabolite MHPG. To ensure the selectivity of DSP4, the contents of dopamine (DA), serotonin (5-HT) and its metabolites (DOPAC and 5-HIAA, respectively) in MPOA were evaluated. Adult female rats were ovariectomized followed by bilateral microinjection of 0.25 uL of vehicle or DSP-4 at doses of 1 or 10 ug/0.25uL in MPOA. At day 15, the rats were decapitated at 9 a.m, the trunk blood was collected for LH and FSH measurements by RIA and the brains were removed for measurements of neurotransmitters in MPOA and MBH by HPLC-ED and GnRH in MBH by RIA. In MPOA, both doses reduced NA content, but only 10 ug of DSP4 reduced MHPG. As expected, there were no changes on NA and MHPG content in MBH and on DA and 5-HT turnover in MPOA. Both doses reduced plasma LH and increased GnRH content in MBH. These results are in accordance to those after LC electrolytic lesion. However, here, denervation is confined to MPOA preventing other target areas of LC to be impaired as occurs by the use of electrochemical lesions.

Neuroendocrinology and Neuroimmunology
Poster Number 183 / Session I

Effects of valproic acid on the postnatal brain

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Prenatal exposure to valproic acid (VPA) can be used in mice as a model of autism. Autism is a neurodevelopmental disorder characterized by impediments in social interaction and by stereotyped or restrictive behaviors. Typically, these symptoms appear during the first years of childhood. Previous studies have shown a link between autism and neuroinflammation, so we hypothesized that central inflammatory processes and glial activation in particular could be responsible for the behavioral phenotype. In line with this, we found an activated glial state in the cerebellum and the hippocampus of adult VPA mice. The aim of this work is to identify the specific time window when inflammation appears in the VPA postnatal brain and to study the correlation with the behavioral effects that we observe. We are characterizing the astro and microglial state in the early postnatal period (from P7 to P42) by means of immunohistochemical analysis. Additionally, we will evaluate the inflammatory response by measuring corticosterone levels after an LPS challenge. The identification of a critical window when inflammation is altered in VPA mice will allow us to test the specific hypothesis of whether modulating inflammation during the postnatal period can revert the prenatal effects of VPA on social behavior.

Neuroendocrinology and Neuroimmunology

Poster Number 184 / Session II

ENRICHMENT ENVIRONMENT REVERT DELETERIOUS EFFECTS OF PRENATAL RESTRAINT STRESS ON GLUCOCORTICOIDS RECEPTOR IN HIPPOCAMPUS AND LYMPHOID CELLS OF ADULT MICE.

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Stress during pregnancy can impair behavioral responses in the adult offspring and some of these effects are associated with alteration in the HPA axis response. Also, we had shown that during neurodevelopment, C57Bl/6 female mice have increased vulnerability to the deleterious effects of stress on learning and memory. Herein, we are presenting a role of enrichment environment on prenatal and adult restraint stress. For this purpose, pregnant mice were restrained 2 hours daily, since gestational day 14 until delivery. The prenatally restraint stressed offspring (PRS) were expose at 3 months of to acute (2h) or chronic (three-week) restrain stress. We found that female PRS showed poor memory performance as compared to matched control in the habituation to an open field test. Moreover there was an increase in corticosterone plasma levels and in glucocorticoid receptors in hippocampus and lymphoid cells from PRS female mice. In addition an altered HPA response after acute and chronic stress exposure was observed in PRS mice. Enrichment environment reverses the alteration observed in PRS mice. We conclude that PRS induce an alteration of HPA axis with an altered response to acute and chronic stress exposure in the adult life. The HPA response is restored by enrichment environment. UBACYT 2002010010633.

Neuroendocrinology and Neuroimmunology

Poster Number 185 / Session III

Peripheral and central exacerbated inflammatory responses in a mouse model of autism spectrum disorders

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Autism spectrum disorders (ASD) are severe neurodevelopmental disorders with a prevalence estimated in 9 per 1000 population. The symptoms of autism involve significant impairments in social, communicative, and cognitive functioning. Based in several studies, which associated brain inflammation with ASD, we hypothesized that the glial response represents an underlying common factor in the different proposed etiologies of ASD. To investigate this, we used a mouse model of autism: the prenatal exposure to VPA. Our results show that mice exposed prenatally to VPA have reduced social interaction and increased anxiety-related behavior in adulthood. Prenatal exposure to VPA also led to an exacerbated response to an inflammatory stimulus in adulthood, observed as an increment in the expression of pro-inflammatory cytokines and as a bigger activation of the hypothalamus-pituitary-adrenal axis. This exacerbated response was also found in the brain: VPA-exposed animals showed glial activation in different brain zones and an exacerbated inflammatory central response to a peripheral LPS challenge. These results demonstrate a basal and subclinical inflammatory state in the brains of VPA-exposed animals and an increased reactivity to adult inflammatory stimuli. We therefore propose that the neuroinflammation observed in human postmortem studies represent an actual ASD phenotype. We will next evaluate to what extent this inflammatory reactivity contributes to the behavioral phenotype.

Neuroendocrinology and Neuroimmunology

Poster Number 186 / Session I

INFLUENCE OF ENRICHED ENVIRONMENT IN THE DELETEROUS EFFECT OF PRENATAL STRESS ON BEHAVIOUR. INVOLVEMENT OF NEUROTROPHINS

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It was described that Prenatal Stress (PS) can influence the behavior of the offspring. The aim of this work was investigate alterations in behavior and neurotrophins expression and the influence of enriched environment in adults animals subjected to PS. For this purpose, pregnant BALB/c mice were individually restrained 2 hour a day, since gestational day 14 until delivery. A group of stressed offspring mice were exposed to enriched environment after weaning. Animals were tested at 3-months of age. Results shown that PS induces an alteration in the performance in the open field and Barnes maze task. A decrease in BDNF levels by Real-Time PCR and western blot was observed in hippocampus and lymphocytes. Moreover, these animals showed an increase vulnerability to adult chronic stress exposure respect to normal animals. Enriched environment improve the performance in behavioral test in both PS non-exposed and exposed to chronic stress animals. These results indicate that the exposure of enriched environment counteracts deleterious effect induced by PS. In addition, it is possible postulate that the lymphoid cell could be a peripheral marker of the alterations that occur in the hippocampus.
UBACYT 2002010010633.

Neuroendocrinology and Neuroimmunology

Poster Number 187 / Session II

HYPOTHALAMIC INSULIN-LIKE GROWTH FACTOR-I GENE THERAPY PROLONGS REGULAR ESTRAL CYCLICITY IN MIDDLE-AGED FEMALE RATS

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In the female rat, reproductive aging is characterized by a gradual disruption of regular estrous cyclicity at middle age (9 mo) caused by the alteration in the secretion of gonadotropin releasing hormone (GnRH). There is evidence suggesting a regulatory role for insulin-like growth factor type I (IGF-I) on reproductive function, possibly due to fact that IGF-I regulates estradiol-dependent afferent signals to GnRH neurons or GnRH neuronal responsiveness to afferent inputs. To assess the effectiveness of long-term IGF-I gene therapy in the medial basal hypothalamus (MBH) of adult female rats to extend regular cyclicity and preserve ovarian structure when the animals reach middle age, we used three groups of female rats of 34 weeks of age: one group of intact rats, and two groups injected in the MBH with either a bicistronic adeno-associated vector (AAV) carrying the genes for IGF-I and red fluorescent protein (DsRed2), or a control AAV only carrying the gene encoding DsRed2. In order to assess the patterns of estrous cyclicity, daily vaginal smears were taken throughout the study which ended atl 49.5 weeks of age. We observed that while most of the rats injected with AAV-IGF-I-DsRed2 had a normal estrous cyclicity until the end of the experiment, the intact and DsRed groups showed a high percentage of acyclic rats at the end of the study. These results suggest that increased levels of IGF-I in MBH extend normal ovarian function in middle-aged female rats.

Sensory Systems

Poster Number 188 / Session III

Differential visual adaptation mechanisms in an arthropod.

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Crabs are highly visual animals that display complex visually guided behaviours. They have well-developed compound eyes located on mobile stalks, containing an important part of their nervous systems. The massed presentation of a visual danger stimulus elicits animal escape which declines after a few stimulus presentations. By using calcium imaging techniques, we had revealed that this behavioural change is due to a decrease in the activity of columnar visual neurons and that this is the first site of sensory adaptation in the visual nervous system. Optic ganglia have a retinotopic organization. Here we show that visual training in one region of the visual field only produces adaptation of the columnar neurons mapping the retina area. If at the end of visual training a second retina area is stimulated, the response of the matching columnar elements remain unaltered. In this way, the observed differential adaptation allows the system to keep responding to a novel stimulus appearing in a new receptive field. Considering these results and that visual processing is segregated into different visual channels (colour, direction of motion, etc.) our goal now is to study if sensory adaptation provoked in one particular channel is transferred to another one. In other terms, are crabs able to generalize these features inside the same receptive field? At this respect we will just present preliminar results.

Sensory Systems

Poster Number 189 / Session I

Understanding the roles of the efferent system after acoustic trauma.

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The transduction of sound is inhibited by efferent cholinergic neurons projecting from the brainstem and synapsing directly on hair cells. Efferent innervation undergoes extensive modification early in development, i.e. shortly after the onset of hearing in mice (P11), synaptic contacts between efferent fibers and inner hair cells (IHCs) are lost. However, it is not clear if efferent synapses are modified by age, hearing loss or both. Here, we tested how efferent innervation is rewired after noise trauma. We evaluated if exposure to loud sounds (1-16 kHz, 100 dB SPL, 30min) in mature animals can trigger a re-innervation. We used confocal immunohistochemistry to visualize efferent nerve terminals and found disorganized efferent terminals after acoustic trauma comparing to controls. We measured auditory brainstem responses (ABR), which reflect synchronized discharges from neurons along the auditory pathway and distortion product otoacoustic emissions (DPOAEs), to test outer hair cells function. After acoustic trauma, animals showed large ABRs and DPOAEs threshold shifts. Suprathreshold ABR amplitudes were reduced, even in animals with almost normal threshold sensitivity. These findings will contribute to the understanding of how normal hair cell function is affected by acoustic trauma and the role of the efferent system.

Sensory Systems

Poster Number 190 / Session II

Strategy for determination of the orientation of an object by the somatosensory system

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The present experiment was design in order to obtain information about the strategy that the somatosensory system uses to obtain information about a rotated object. Two experiments were developed, each with 10 participants divided in two groups, left-handed and right-handed. In the first experiment, a metallic ellipsoid object was rotated in one of 11 possible angles (-32, -16, -8, -4, -2, 0, 2, 4, 8, 16 y 32°), the participants were blindfolded and their task consisted on touching the object to determine in which direction it was rotated, either clockwise or counter-clockwise, once determined their responses where registered using a mouse and then they proceeded to the next trial. Each participant executed 144 trials for each angle during 4 sessions using the left hand for one half and the right hand for the other half of the trials. The number of correct responses was recorded along with the object's exploration time. The second experiment was very similar to the first, except that the time the participants had to explore the object was restricted. It vary from 0 to 2s in exponential growth, each participant executed 120 trials for each angle. The results are discussed in terms of the accumulation to bound and the independent sampling model.

Sensory Systems

Poster Number 191 / Session III

Differential distribution of CB1 and CB2 receptors in adult rat retina.

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Although CB1 receptor has been reported in rat retina, little was known about the localization of CB2 receptors. In the present work we examined the immunostaining distribution of both receptors in adult rat retina. Male Sprague Dawley rats were anesthetized and fixed by perfusion with 4 % paraformaldehyde solution. Eyes were removed and cryostat sections were processed by immunocytochemistry using either a CB1 or a CB2 rabbit polyclonal antibody. CB1 immunoreactivity (IR) showed a dotted pattern staining in inner nuclear and inner plexiform layers (IPL). Neurons (horizontal and amacrine cells) were not clearly identified in inner nuclear layer. Surprisingly, cells of ganglion cell layer (GCL) were immunostained. CB2 was localized in retinal pigmented cells, in horizontal and amacrine cells. CB2-IR was also observed in IPL and strong labeled cells were detected in GCL. The results demonstrated two different staining patterns for CB1 and CB2 in adult rat retina. Further work is needed to better characterize the colocalization of cannabinoid receptors in retinal cell populations and to know the physiological relevance of this neurotransmitter system which may be target for future therapeutic interventions. (Supported by UBACYT 200-201001-00329).

Sensory Systems

Poster Number 192 / Session I

Measuring and modeling experience dependent plasticity in sensory processing

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Animals are immersed in a world of countless stimuli. To deal with the excess of information they have systems that process the sensory afference and detect the relevant information. In the present work we ask how this detection is optimized when the classification “relevant or irrelevant” depends on the experience of each individual. How the sensory processing is adjusted in a dynamic and reversible way to help distinguishing the relevant information from the noise? The olfactory system of insects provides a good model for this study. Odors in nature are complex mixture, in which irrelevant components may hide the presence of relevant ones. We show results that put in evidence how the bees distinguish the presence of a rewarded component in a mixture. We performed calcium imaging in the antennal lobe of bees (the first processing center for olfactory information) and measured the neural representation of complex mixtures and pure components. We found that the relative weight of the components in the representation of the mixture depends on the experience of the animals with the components. The results do not show impact of the training in the representation of the pure odors. Based on these results we present a mathematical model that replicates the antennal lobe connectivity and reveals potential sites of plasticity that may account for the experimental results.

Sensory Systems
Poster Number 193 / Session II

Reconstruction of firing rate from Ca2+ fluorescence signal

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In this study, we present a simple algorithm for the reconstruction of firing rate from Ca2+ fluorescence signal. The basic idea of this method is that action potentials (APs) open voltage-gated Ca2+ channels and produce unitary Ca2+ transients with a fast rise and a stereotyped, usually exponential, decay. During trains of APs, individual transients summate and generate complex temporal variations in Ca2+ concentration. These processes can be approximated by a first order linear system and the Ca2+ signal can be generated by a convolution of the AP train with the waveform of the unitary Ca2+ transient. We simultaneously recorded voltage and fluorescence signal for different giant neurons in the crab Neohelice granulata and investigated whether a neuron discharge can be extracted with reasonable precision from single trials using dF/F recorded. To quantify the accuracy of the proposed algorithm, we calculate the cross-correlation between the measured and the predicted neuronal firing rate. We obtained maximum correlation values above 0.9 in all neurons tested. We conclude that this method of firing rate reconstruction, from spiking neurons, is simple and accurate.

Synaptic Transmission and Excitability
Poster Number 194 / Session III

ATP modulates synaptic activity at the efferent-inner hair cell synapse in the developing inner ear

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Before the onset of hearing (Postnatal day (P) 14 in mice) mammalian inner hair cells (IHCs) are transiently innervated by medial olivocochlear (MOC) efferent fibers. The release of acetylcholine (ACh) by these fibers activates α9α10 nicotinic receptors coupled to SK2 calcium-activated potassium channels, leading to inhibitory post synaptic currents (IPSCs) at the IHCs. During this developmental period, IHCs fire spontaneous sensory-independent action potentials most likely essential for the refinement of tonotopic maps upstream in the auditory pathway. Recent studies suggest that this spontaneous activity is driven by ATP released from cochlear supporting cells. As ATP is a widespread modulator of neurotransmission, we investigated if it also regulates the MOC-IHC synapse. IPSCs, evoked by electrically stimulating MOC fibers, were recorded in mice IHCs from acutely isolated organs of Corti at P9-P12. ATP (100 μM) reversibly decreased the quantal content of evoked release and the frequency of spontaneous IPSCs (~50 %). In addition, spontaneous synaptic currents amplitude was also reduced (23 %). These results suggest that ATP probably modulates the MOC-IHC synapse through both pre and post synaptic mechanisms. We are currently studying which ATP receptors are responsible for this modulation.

Synaptic Transmission and Excitability
Poster Number 195 / Session I

Neuronal and endothelial ultrastructural alterations in a rat model of perinatal asphyxia

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We previously observed in a rat model in which we perform perinatal asphyxia (PA) by transient immersion in water at 37˚C of fetuses still contained in utero obtained by histerectomy, several long-term (more than 4 months of age) alterations in the brain as damage in cortical lamination and neuronal migration in frontal cortex and hypolocomotion in male rats, with an decrease in their exploratory behaviour. Images obtained by using Golgi technique showed in the cortex of AP rats tortuous apical piramidal dendrites with neurofilament altered distribution. Furthermore a decrease in spines was observed in their lateral dendritic processes. In the present work we studied the ultrastructure of frontal cortex of 5 PA rats vs 4 frontal cortex of control animals of 21 postnatal days (short-time). In approximatelly 15-20 % of PA cortex we observed neuronal changes as granular endoplasmic reticulum hyperthrophy and cellular swollen. In 3 animals we found picnosis and nuclear fragmentation. In all PA frontal cortex we found ultrastructural alterations as tight junction desorganization and multiple vesicles in the cytoplasm of endothelial cells. All this changes were not observed in control cortex. We conclude that frontal cortex of animals that suffered PA is affected early with a blood brain barrier alteration which could explain neuronal lesions a the bradikinesia observed in male PA rats when studied with open field test.

Synaptic Transmission and Excitability
Poster Number 196 / Session II

Two-photon activation of dendritic spines with caged dopamine.

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We introduce a novel caged dopamine compound (RuBi-Dopa) capable to be released with visible light (blue-green) and IR in a two-photon regime. We combine two-photon photorelase of RuBi-Dopa with two-photon calcium imaging for an all-optical imaging and manipulation of individual dendritic spines in living brain slices.

Synaptic Transmission and Excitability
Poster Number 197 / Session III

INVOLVEMENT OF THE GABAERGIC SYSTEM IN THE GLUTAMATE RELEASE MODULATION OF FRONTAL CORTEX SYNAPTOSOMES OF RATS WITH EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

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EAE is a model that mimics many of the clinical and pathological features of multiple sclerosis. We have previously found a significant reduction in the GABA regulation of the glutamate release from synaptosomes of EAE rats during the acute stage of the disease. Since GABA is an essential neurotransmitter involved in the maintenance of neuronal homeostasis, in this work we evaluate the effect of GABAergic agonists in the modulation of glutamate release of control and EAE rat frontal cortex synaptosomes and their effect on the synapsin I phosphorylation. The results show that GABA agonists contribute to a decrease in glutamate release and synapsin phosphorylation on site P-3. For GABA, Muscimol (GABAA agonist), Baclofen (GABAB agonist), Gabapentin (calcium channel blocker), exists a correlation between the decrease in synapsin phosphorylation and Ca+2-dependent glutamate release. In the case of the benzodiazepines Diazepam and Clonazepam, GABAA allosteric agonists, the decrease in synapsin phosphorylation is higher than the effect in glutamate release. The effect of the GABA agonists in some cases was partially blocked by picrotoxin. In conclusion, these results indicate that the GABAergic system modulation is altered in the acute phase of EAE depending on the activated pathway.

Synaptic Transmission and Excitability
Poster Number 198 / Session I

Differential effects of cocaine and methylphenidate on GABA release from thalamic reticular nucleus

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Methylphenidate (MPH), a drug used to treat children diagnosed with attention deficit/hyperactivity disorder, shares mechanistic similarities to cocaine (COC), but its effects on GABAergic transmission in sensory thalamic nuclei are unknown. We compared COC and MPH effects on GABAergic projections between thalamic reticular and ventrobasal (VB) nuclei. We subjected mice (P18-30) to binge-like Coc and MPH acute and sub-chronic administrations, and evaluated locomotion and patch-clamp GABA-A-mediated currents from VB neurons in thalamocortical slices. Sub-chronic COC-mediated effects on hyperlocomotion were stronger than MPH effects. Sub-chronic COC and MPH altered paired-pulse and spontaneous GABAergic input differently. The effects of COC on evoked paired-pulse GABA-A mediated currents changed from depression to facilitation with the duration of the protocols used, while MPH induced a constant increase throughout administration protocols. Our results suggest that COC and MPH produced distinct presynaptic alterations on GABAergic transmission. Differential effects of COC on postsynaptic VB calcium currents might explain deleterious COC effects on sensory thalamic nuclei. These results also help to understand the impact of MPH repetitive administration on sensory thalamic nuclei. FONCYT-PICT 2007-1009, PICT 2008-2019 & PIDRI-PRH 2007 (Dr. Urbano), CONICET- PIP 2011-2013-11420100100072 (Dr. Bisagno), and by NIH grants P20 GM103425-09, and R01 NS020246-25 (Dr. Garcia-Rill).

Synaptic Transmission and Excitability
Poster Number 199 / Session II

Effects of the carbonic anhydrase inhibitor acetazolamide on transmitter release at the mouse neuromuscular junction.

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Acetazolamide (AZ) is known to inhibit the action of carbonic anhydrase, an enzime responsible for regulating the extra- and intracellular pH (Maren T. H., 1967). This drug is used as an anticonvulsant and for treatment of episodic ataxia type-2 patients (Robbins et al., 2009), but its mechanism of action is still unknown. To gain insight on this subject, we studied the dynamics of stimulated vesicular exocytosis using fluorescence assays in ex vivo levator auris longus muscles. The drug was applied to the bath solution at a concentration of 100μM, which is found in the pharmacological range. Motor end-plates were loaded by stimulation of the neuromuscular junction (NMJ) at 20Hz in the presence of FM2-10 dye and, after washing, were unloaded at 50 Hz. Pictures were acquired every 3s for at least 700s. Unloaded control NMJ retained only a 16±2% of the initial fluorescence; in contrast, AZ treated NMJ retained 62±14%, suggesting that AZ affects the evoked induced exocytosis. Preliminary electrophysiological experiments performed in low Ca2+ and high Mg2+ solution showed, in agreement with the above results, a 58% increase in evoked end-plate potentials failures.

Synaptic Transmission and Excitability

Poster Number 200 / Session III

ADENINE NUCLEOTIDES INDUCE PRESYNAPTIC INHIBITION OF ACETYLCHOLINE RELEASE BY ACTIVATING P2Y 13 RECEPTORS AT THE MOUSE NEUROMUSCULAR JUNCTION

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At the mouse neuromuscular junction (NMJ), we have demonstrated that ATP reduces ACh release by activating P2Y receptors (R) coupled to Gi/o protein (De Lorenzo et al 2006). Among the 8 P2YR subtypes identified, only P2Y12 and P2Y13 are Gi/o protein-linked and adenine nucleotide-activated receptors. Our aim was to identify the P2YR subtype/s involved in the presynaptic inhibition induced by ATP (phrenic-diaphragm preparations, CF1 mice). We found that the preferential agonist for P2Y12/13R, 2-MeSADP reduced MEPP frequency to 55 % of control values, being more potent in this action than ADP and ATP. This effect was prevented by the selective P2Y12/13R antagonists, 2-MeSAMP and AR-C69931MX. When preparations were incubated with the specific P2Y13R or P2Y12R antagonists (MRS2211 or MRS2395, respectively), we observed that MRS221, but not MRS2395, occluded 2-MeSADP action. Moreover, MRS2211 also abolished the effect of the selective P2Y13R agonist IDP. Similar results were observed when the inhibitory action of 2-MeSADP on EPP amplitude was analyzed in the presence of the antagonists. Immunohistochemical studies confirmed the presence of P2Y13R at the NMJ. These results suggest that at motor nerve terminals, the modulatory effect of ATP/ADP on ACh secretion is mediated by P2Y13R.

Synaptic Transmission and Excitability
Poster Number 201 / Session I

A Bayesian approach for fitting integrate-and-fire model parameters to electrophysiological data obtained from adult-born neurons

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We have recently shown that immature granule cells (GCs) of the adult dentate gyrus display a low threshold for activation rendered by their high excitation/inhibition balance [1,2]. To better understand the underlying intrinsic and synaptic mechanisms we now present and apply a data integrative method for fitting integrate-and-fire model parameters. We show how electrophysiological data on intrinsic and synaptic properties can be combined into a single-neuron model capable of predicting the output to a given input. The data consists of 1) spiking frequency measured against varying injected current and 2) spike trains of GCs observed as a response for entorhinal inputs [2]. For the latter, post-synaptic excitatory and inhibitory currents are collected and used for the parameter fitting and prediction. Our results show that the presented Bayesian method succeeds well in the integrative fitting of the data and that qualitatively correct predictions can be obtained using the model, despite the simplicity of integrate-and-fire dynamics. References: [1] Mongiat et al, PLoS One, 4(4): e5320, 2009. [2] Marín-Burgin et al, Science, 335(6073):1238-42, 2012.

Synaptic Transmission and Excitability

Poster Number 202 / Session II

EXOCYTOSIS AND RECOVERY OF EXOCYTOSIS AFTER ACTION POTENTIAL LIKE STIMULUS IN CHROMAFFIN CELLS: A NEW FAST RELEASABLE AND RECYCLABLE VESICLE POOL?

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The immediately releasable pool (IRP) is group of vesicles highly coupled to P/Q Ca2+ channels. It is expected that action potentials applied at low frequency evoke the exocytosis of vesicles from this pool. In this work we analyzed the origin of vesicles released by an action potential like stimuli (APs), and the following process or exocytosis recovery. The application of single APs induced a capacitance increase of 11±2 fF (8 vesicles). When IRP was assessed 200 ms after APs application, IRP exocytosis was decrease in a magnitude similar to APs associated exocytosis (APAE). However, while IRP was replenished with a τ=7±1s the APAE was recovered much faster (τ=1±0.1s), from similar relative values at time zero. We wonder about the mechanism of APAE recovery: it may be vesicle mobilization from IRP or recovery in situ by kiss and run. When IRP was completely depleted by a 50 ms depolarization, APAE recovered with a kinetic similar to IRP. Finally, when we inhibited endocytosis by dynasore 80 µM or nitrendipine 10 µM application, APAE recovery was not modified. We conclude that in our experimental conditions (room temperature, 5 mM Ca2+) APAE can sustain secretion at low frequencies of APs (0.2 Hz), and it would represent a vesicle pool directly fed by vesicles of IRP.

Synaptic Transmission and Excitability

Poster Number 203 / Session III

Is DMT1 involved in myelination?

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Loss of axonal contact in isolated Schwann cells (SC) in vitro or after nerve injury in vivo leads to de-differentiation of these cells. We have described that holotransferrin(hTf) and iron prevents this de-differentiation while apotransferrin is unable to avoid it; plus, after iron treatment, intracellular signals towards differentiation become activated. Iron and hTf effect suggests their participation in the axonal signal that enables SC maturation and survival. Whereas Tf-mediated iron uptake is considered the main route, there is evidence for Tf-independent mechanisms. In the present work we demonstrate the existence of a divalent metal transporter(DMT1)greatly described in literature as an iron metabolism key player, but never before within the PNS context. The presence of DMT1 was demonstrated in sciatic nerve homogenate, isolated rat myelin and cultured SC by Western Blot and confirmed through its co-localization with S-100 by immunocytochemistry. In addition, the existence of its mRNA was verified by RT-PCR. DMT1 mRNA was found all along SC progeny. In sciatic nerves of rats previously submitted to crush; DMT1 expression was increased 14 days post injury (PI); at 21 and 35 days PI levels did not return to control ones. These data lead us to postulate DMT1 involvement in ensuring the provision of iron in the PNS and to confirm the existence of a Tf independent iron uptake mechanism, validating the role of iron in the axonal signal, essential for myelination in the PNS

Synaptic Transmission and Excitability
Poster Number 204 / Session I

EFFECTS OF TEMPERATURE ON THE EXOCYTOSIS INDUCED BY ACTION POTENTIAL LIKE STIMULI

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The immediately releasable pool (IRP) of chromaffin cells, is a group of ready releasable vesicles highly coupled to the voltage dependent P/Q-type Ca2+ channels, which is secreted by brief stimuli (Álvarez, et al.). In this work, we applied action potential like stimuli (APs) to analyze the temperature dependence of Ca currents (ICa2+), exocytosis and recovery of the vesicle pool released by this type of stimulation. The ICa2+ induced by APs were 106.1 ± 16.3 pA and 259.0 ± 25.7 pA for 20 ºC and 25ºC, respectively, while at 15ºC we did not observed significant ICa2+. The decrease of ICa2+ at low temperatures may be explained by changes in the activation time constant observed during 50 ms square depolarizations (2.75 ± 0.13 ms, 1.39 ± 0.21 ms and 0.86 ± 0.05 ms for 15 ºC, 20 ºC and 25ºC, respectively). The capacitance increases induced by APs at 20ºC and 25ºC, were 5.6 ± 0.3 fF and 7.4 ± 0.9 fF, respectively. Finally, we studied the recovery of exocytosis after the application of single action potentials. The time constants for this process were 2.37 ± 1.37 and 1.06 ± 0.48 sec. for 20ºC and 25ºC respectively. In conclusion, our results indicate that the Ca2+ currents, exocytosis and its recovery occur in a temperature dependent fashion.

Synaptic Transmission and Excitability
Poster Number 205 / Session II

Membrane properties are modified in seasonal adaptation to temperature in the electric fish Brachyhypopomus gauderio

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Electric organ discharge (EOD) of gymnotiforms is part of a sensory system and a communication signal. EOD waveform inform to coespecifics about its sexual maturity. Sex steroids during breeding season differenciate sexually the EOD and make its waveform resistant to changes caused by rapid increases of temperature. The negative/positive ratio of the biphasic EOD of B. gauderio is reduced to almost 0 after a sudden increase of temperature from 20°C to 30°C and must reach a value of at least 0.5 after 15 minutes for to be considered a fish as thermoresistant. Species specific EOD waveform is due to: central mechanisms, organization of the electric organ (EO), membrane properties of the electrocytes (EC) and electrical properties of surrounding tissues. Two-electrodes voltage-clamp was performed in EC from isolated EO after blockage of main Na+, K+ and Ca2+ currents. In these conditions and under controlled temperature we recorded currents elicited by voltage steps of 300 ms from -120 to + 80 mV. Outward currents elicited at +80mV at 30°C increased in average about 20% respect to that elicited at 20°C. During breeding season, when fish EOD was temperature resistant, this average current returned to the same value of that recorded at 20°C in 15 minutes. During non breeding season these average outward currents remained increased when temperature was mantained at 30°C. The thermoresistant EOD in breeding fish is due in part to changes in temperature sensitive currents in EC.

Synaptic Transmission and Excitability
Poster Number 206 / Session III

Control of excitability in striatal cholinergic interneurons: mechanism underlying IsAHP

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Parkinson's disease is a neurodegenerative disorder caused by nigrostriatal dopaminergic neuron loss. Acetylcholine released by a small population of tonically active interneurons (ChIs), is a main modulator of striatal function. Tonic activity in ChIs depends on intrinsic mechanisms. Action potentials open K+ channels, either KCa or Kv, leading to an afterhyperpolarization (AHP) with three phases: fAHP, mAHP, and sAHP. Molecular mechanisms that mediate IsAHP in ChIs are still unknown, but it is supposed to be Ca2+ dependent. Previous work shows that a reduction of IsAHP results in hyperactive ChIs in a rat model of Parkinson's disease, which is seen as a lack of "accommodation". Thus, IsAHP may be a novel target to treat the hypercholinergic state in Parkinson's disease. Here we study the maturation and pharmacology of IsAHP in ChIs from mouse brain slices. Accommodation and IsAHP in ChIs were insensitive to UCL2077, a blocker of atypical KCNQ K+ channels, but they were strongly reduced by margatoxin, a blocker of voltage-gated K+ channels with selectivity for Kv1.3 channels. Thus, our data suggest a novel voltage-dependent component of IsAHP in ChIs which needs further validation as a therapeutic target in animal models of Parkinson's disease.

Synaptic Transmission and Excitability

Poster Number 207 / Session I

Differential effects of methylphenidate and cocaine binge on calcium dynamics of thalamic ventrobasal neurons in mice

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Cocaine (Coc), but not methylphenidate (MPH) binge administration has been described to enhance T-type calcium currents in the Ventrobasal nucleus (VB). However, the effects of these stimulants on intracellular [Ca2+] dynamics are unknown. Mice (male C57BL/6, P18-23) received one Coc or MPH binge (3x15 mg/kg i.p., 1h apart) or saline. VB neurons were patch-clamped using an egta-free intracellular solution with the high-affinity Ca2+ indicator bisfura-2 (60μM). Fluorescence was measured in somas and proximal dendrites during voltage steps from -70mV to -30mV or -10mV to maximally activate T- or P/Q-type Ca2+ currents. In dendrites, only MPH induced an increase in peak Ca2+ transients at -10mV and -30mV. Area under Ca2+ transients was bigger in dendrites at -30mV for the MPH group (n=12) compared to Coc (n=5; p=0.024). Dendrites/soma area ratios were bigger for the MPH group than for Coc or saline groups at -10mV and -30mV (-10mV: MPH 2.3±0.7, n=12; Coc 0.5±0.1, n=5; saline 0.7±0.1, n=4; -30mV: MPH 2±0.4; Coc 0.3±0.04; saline 0.7±0.3), indicating a larger entry of Ca2+ in proximal dendrites, where P/Q-type channels are known to mediate gamma band oscillations. These results suggest that MPH might be more effective than Coc in enhancing dendritic synaptic integration onto VB neurons. FONCYT-PICT 2007-1009, PICT 2008-2019 & PIDRI-PRH 2007 (Dr. Urbano), CONICET- PIP 2011-2013-11420100100072 (Dr. Bisagno), NIH grants P20 GM103425-09, R01 NS020246-25 (Dr. Garcia-Rill).

Poster Number 208 / Session II

Indicators and oxidative stress in experimental cerebral vasospasm

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Biomarkers measurable in the blood may provide a new window into the pathophysiology of cerebrovascular damage. Clinical trials have been performed to establish the sensitivity and specificity of biomarkers for routine use in this condition. We studied two inflammatory biomarkers are plasma fibrinogen and nitric oxide in male Wistar rats, which were divided into three groups: group (I) control, group (II) with acute vasospasm induced by transient cerebral artery occlusion half during 60 minutes and the group (III) with vasospasm induced by transient occlusion evolved middle cerebral artery for 60 minutes. Was induced by transient cerebral vasospasm by intraluminal occlusion of the middle cerebral artery with 4-0 mononylon thread. The determination of fibrinogen showed a significant increase of fibrinogen to vasospasm groups with (II) (356 ± 3.36), and (III) (373 ± 2.01) (II vs. III: $p < 0.01$) compared with control group (I) (191 ± 1.5) (I vs II: $p < 0.001$; I vs III: $p < 0.001$), no significant changes in fibrinogen in groups (II) and (III). The dosage of nitric oxide bioavailability expressed the same, similar in both groups (II) (17.49 ± 0.83) and group (III) (18.05 ± 1.40) (II vs. III: NS), however there was no difference between the two groups (II) (III) in relation to the control group (I) (I vs. II: $p < 0.01$ vs group I group III: $p < 0.01$).

Cognition, Behavior, and Memory
Poster Number 209 / Session III

GLUCOSE CONSUMPTION AND METABOLIC ACTIVITY ON LATERAL SEPTUM

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Glucose is one of the most important nutrients of the brain, and its consumption could be associated whit levels of brain metabolic activity. The aim of this work was to study whether or not this possible association could be of any help in order to evaluate the effect of different reactives on metabolic activity of lateral septal nucleus (LSN), our region of interest regarding memory processes. Whole LSN were incubated at 37°C with 200 µl Krebs buffer and treated with: 1) Saline; 2) Pregnenolone (Preg) 12µM; 3) Pregnenolone sulphate (PS) 12µM; 4) Lidocaine (Lid) 2 µg/µl; 5) Ap7 1 µg/µl and 6) Bicuculine (Bic) 3 µM. Glucose concentrations were measured at 0, 60 and 120 minutes. Our results showed that PS and Bic have a negative effect while Lid had a positive effect over metabolic activity. Preg and AP7 showed no effect compared to control group. This simple but effective method could be useful for several purposes, such as getting an eventual relationship of levels of neuronal activity and memory performance during diverse behavioral paradigms.

Neurochemistry and Neuropharmacology
Poster Number 210 / Session I

Role of Wnt/b-catenin signaling pathway in the expression of cocaine induced sensitization

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Wnt factors are cysteine rich secreted proteins that interact with their receptors: Frizzled, Ryk, and Ror. As a result of the interaction, Dishevelled (DVL) is activated, and consequently, one of three pathways: Wnt/b-catenin, Planar Cell Polarity, or Wnt/calcium pathways. Wnt signaling pathways are essential for development of the mammalian brain. However little is known regarding its role in adulthood. Our main goal is to elucidate if the Wnt/b-catenin signaling pathway participates in cocaine sensitization. Therefore, adult male Wistar rats received cocaine injections daily for a week and then a challenge three weeks later. Locomotor activity was recorded on Day 1, 7 and 28. Our rats chronically treated with cocaine showed a significant increase in locomotor activity when comparing Day 28 to Day 1, as it was previously demonstrated. Twenty four hours after cocaine challenge on Day 28 rats were sacrificed, and brains areas were dissected to study b-catenin expression levels. Our data showed changes in b-catenin expression only in the Nucleus Accumbens (NAcc) of animals that showed cocaine sensitization on Day 28, while no changes were found in Prefrontal Cortex. So far our data suggests that b-catenin in NAcc is involved in the expression of cocaine induced sensitization.

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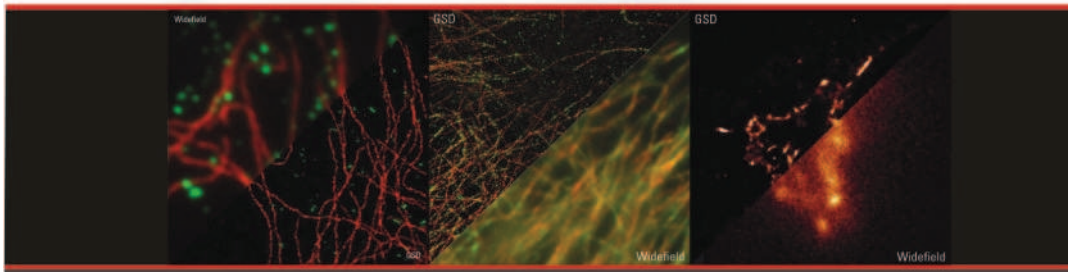

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