



Sociedad
Chilena
de Neurociencia

X Annual Meeting

Hotel Villa del Río, October 1-4, 2014
Valdivia, Chile





A message from the President

The Sociedad Chilena de Neurociencia (SCN) has organized its 10th annual meeting. Our Society was born nearly 10 years ago, with a conference by Dr. Ranulfo Romo, a renowned scientist from the Universidad Autónoma de México (UNAM), who was specially invited for the occasion. He spoke to a large and enthusiastic audience about his research on coding of temporal patterns in the cerebral cortex. The event took place in the auditorium of the Departamento de Biología, Facultad de Ciencias of the Universidad de Chile. The conference was accompanied by the presentation of posters. The same year we held our first Meeting in Termas del Corazón, a beautiful mountain resort North of Santiago. Since then we have grown significantly, and currently the SCN has 139 members, a good number of them young investigators and graduate students. We are very satisfied of the rapid and constant growth of the SCN and of the success of our meetings. We have made every effort to include top conference speakers, many of whom coming from abroad. The symposia, organized by our members, have also been of high quality, each one having at least one foreign speaker. From the very beginning, one of the symposia in all our meetings has been the **Young Neuroscientists Symposium**, where the speakers are advanced graduate students and postdocs from Latin American countries selected according to their merits. The quality of these symposia has always been outstanding. The full expenses of the four speakers have been with funding provided by different generous sources, including the SCN.

In 2012 we joined the other Latin American Societies of Neuroscience belonging to FALAN (Federación de Asociaciones Latinoamericanas de Neurociencia) in Cancún, Mexico, where over 50 Chileans participated. Last year the SCN and SOBLA (Sociedad de Biofísicos Latinoamericanos) held a successful joint meeting in Valparaíso.

We are confident that the 2014 meeting in Valdivia will be a great event, as we have received many more works than ever. The meeting will include 5 superb plenary lecturers, 7 very exciting symposia with 28 presentations covering a wide range of interests in the field, a Round Table about the impact of scientific research in the society, 112 posters and 15 short oral presentations.

We thank all the invited speakers for traveling long distances to take part in the meeting, the organizers of the various activities and all the participants.

On behalf of the SCN Directory, who has organized this Congress, I like to welcome and invite you all to enjoy the meeting and the beauty of Valdivia.

Have a great time!

*Juan Bacigalupo, PhD
President Sociedad Chilena de Neurociencia
October, 2014*

BRIEF PRESENTATION OF THE PLENARY LECTURERS 2014



DR JOHN HILDEBRAND

Foreign Secretary of the U.S. National Academy of Sciences and Regents Professor and Professor of Neuroscience, Chemistry & Biochemistry, Ecology & Evolutionary Biology, Entomology, and Molecular & Cellular Biology.

University of Arizona, USA.

PhD Rockefeller University, USA (L Spector, F Lipmann).

Postdoc Harvard University (E Kravitz).

Some of his numerous awards and prices are: member of the U.S. National Academy of Sciences, the American Academy of Arts and Sciences, Alexander-von-Humboldt Research Prize, Silver Medal of the International Society of Chemical Ecology, Max Mozell Award from the Association for Chemoreception Sciences, Past-President of the International Society for Neuroethology, the International Society of Chemical Ecology and the Association for Chemoreceptor Sciences.

Dr. Hildebrand's research combines anatomical, behavioral, molecular and neurophysiological approaches in multidisciplinary studies of problems of the functional organization, physiology, behavioral roles, and postembryonic development of the olfactory system in insects; chemical and sensory ecology of moth-host plant interactions; sensory neuroethology of feeding, mating, and oviposition; and the neurobiology and behavior of disease-vector insects

Selected publications

Lei H, Chiu H-Y, Hildebrand JG (2013) Responses of protocerebral neurons in male *Manduca sexta* to sex-pheromone mixtures. *J Comp Physiol A* 199:997-1014

Martin JP, Lei H, Riffell JA, Hildebrand JG (2013) Synchronous firing of antennal-lobe projection neurons encodes the behaviorally effective ratio of sex-pheromone components in male *Manduca sexta*. *J Comp Physiol A* 199:963-979

Riffell JA, Lei H, Abrell L, Hildebrand JG (2013) Neural basis of a pollinator's buffet: olfactory specialization and learning in the *Manduca sexta* moth. *Science* 339:200-204 Published online 6 December 2012 [DOI:10.1126/science.1225483]

Hinterwirth AJ, Medina B, Lockey J, Otten D, Voldman J, Lang JH, Hildebrand JG, Daniel TL (2012) Wireless stimulation of antennal muscles in freely flying hawkmoths leads.



DR. ISABEL LLANO

Université Descartes Paris V

Research Director (DR2), Centre National de la Recherche, France

PhD UCLA, USA (F Bezanilla)

Postdoc University of Pennsylvania, USA (C Armstrong)

Her research has aimed at unraveling molecular and cellular aspects of synaptic transmission and intracellular calcium homeostasis in the cerebellum. She studies the molecular profile and spatial localization of ion channels and transmitter-gated receptors in GABA-releasing neurons with focus on molecules governing glutamate. She also investigates calcium signaling in cerebellar neurons, with particular emphasis on activity-dependent calcium signals generated in the axon. Her work involves in vitro and in vivo electrical and imaging recordings.

Selected publications

Rossi B, Ogden D, Llano I, Tan YP, Marty A, Collin T (2012) Current and Calcium Responses to Local Activation of Axonal NMDA Receptors in Developing Cerebellar Molecular Layer Interneurons. PLoS One 7 7(6): e39983

Alcami P, Franconville R, Llano I, Marty A (2012) Measuring the firing rate of high-resistance neurons with cell-attached recording. J. Neurosci 32:3118-3130

Franconville R, Revet G, Astorga G, Schwaller B, Llano I (2011) Somatic calcium level reports Integrated spiking activity of cerebellar interneurons in vitro and in vivo. J. Neurophysiol 106:1793-1805

Collin T, Franconville R, Ehrlich BE, Llano I (2009) Activation of metabotropic glutamate receptors induces periodic burst firing and concomitant cytosolic Ca^{2+} oscillations in cerebellar interneurons. J. Neurosci 29:9281-9291



DR. ALAIN MARTY

Université Descartes Paris V

Director CRNS Laboratoire de Physiologie Cérébrale, France

PhD Ecole Polytechnique (P Ascher)

Postdoc Max Planck Institute Goettingen (E Neher)

Dr Marty has received multiple important international awards and led laboratories at Ecole Normale Supérieure in Paris (1982-1994), Max Planck Institute Goettingen (1994-2000) and Université Paris Descartes (2001-present).

Alain Marty's contributions include the demonstration of a coupling between ion channel permeation and gating in acetylcholine-sensitive channels; a participation in the development of the patch-clamp method (in particular, measurement of cell capacitance; perforated patch recording); the discovery of BK channels in chromaffin cells, and of Ca-dependent Cl channels in

acinar exocrine cells; the discovery of DSI and rebound potentiation (two novel forms of synaptic plasticity at central synapses); the demonstration of multivesicular release at central gabaergic synapses; the description of spontaneous calcium transients in axons and synaptic terminals of central gabaergic neurons.

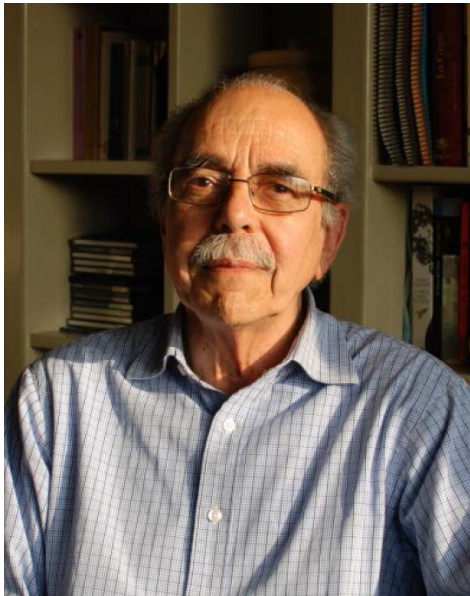
Selected publications

Alcami P, Marty A. (2013) Estimating functional connectivity in an electrically coupled interneuron network. *Proc Natl Acad Sci U S A*. 110:E4798-4807.

Trigo FF, Sakaba T, Ogden D, Marty A. (2012) Readily releasable pool of synaptic vesicles measured at single synaptic contacts. *Proc Natl Acad Sci U S A*. 109:18138-18143

Trigo FF, Bouhours B, Rostaing P, Papageorgiou G, Corrie JE, Triller A, Ogden D, Marty A. (2010) Presynaptic miniature GABAergic currents in developing interneurons. *Neuron*. 66:235-247.

Trigo FF, Chat M, Marty A. (2007) Enhancement of GABA release through endogenous activation of axonal GABA(A) receptors in juvenile cerebellum. *J Neurosci*. 27:12452-12463.



DR. LUIS ROBLES

Programa de Fisiología y Biofísica
Facultad de Medicina, Universidad de Chile
Ph.D. University of Wisconsin, USA

He was Chairman of the Program of Physiology and Biophysics, Faculty of Medicine, Universidad de Chile. He has been Invited Professor in Northwestern University, USA; Université Catholique de Louvain, Belgium; University of Minnesota, USA, University of Wisconsin, USA

Dr Robles' research has been focused on the neurobiology of the mammalian auditory system, with particular emphasis in the cochlear mechanisms and the function of the efferent auditory system on cochlear sensitivity and tuning. His contributions include: the discovery of cochlear non-linearity in mammals; the cochlea

as the origin of the two-tone distortion of the basilar membrane; modulation of cochlear responses during selective attention to visual stimuli.

Selected publications

Verschooten, E., Robles, L., Kovačić, D., Joris, P.X. (2012) Auditory nerve frequency tuning measured with forward-masked compound action potentials. J. of the Association for Research in Otolaryngology 13: 799-817.

Elgueda, D., Délano, P.H. and Robles, L. (2011). Effects of electrical stimulation of olivocochlear fibers in cochlear potentials in the chinchilla. J. of the Association for Research in Otolaryngology 12: 317-327.

Delano PH, Elgueda D, Hamame CM, Robles L (2007) Selective attention to visual stimuli reduces cochlear sensitivity in chinchillas. J Neurosci. 27:4146-53.

Robles L, Ruggero MA (2001) Mechanics of the mammalian cochlea. Physiol Rev. 81:1305-52.

Robles L, Ruggero MA, Rich NC (1991) Two-tone distortion in the basilar membrane of the cochlea. Nature. 349:413-4.



DR. EDWARD TEHOVNIK

Brain Institute, UFRN, Brazil
MIT (2005-2010)
PhD University of Toronto
Postdoc MIT

With the use of methods of psychophysics, scientists have had success in determining how behaving primates process brightness, color and movement (Schiller and Logothetis 1990). Dr. Tehovnik's goal is to use similar psychophysics methods in monkeys to establish the characteristics of electrically evoked perceptions from the visual cortex, with the long-term goal to use this knowledge to design and employ an effective visual prosthesis in the visual cortex of the blind.

Selected publications

Tehovnik EJ, Woods LC, Slocum WM (2013). Transfer of information by BMI. *Neuroscience*. 255:134-146.

Tehovnik EJ, Slocum WM. (2013) Two-photon imaging and the activation of cortical neurons. *Neuroscience*. 245:12-25.

Tehovnik EJ, Slocum WM (2013). Electrical induction of vision. *Neurosci Biobehav Rev* 37:803-818.

Schiller PH, Slocum WM, Kwak MC, Kendall GL, Tehovnik EJ. (2011). New methods devised specify the size and color of the spots monkeys see when striate cortex (area V1) is electrically stimulated.

Proc Natl Acad Sci U S A;108:17809-17814.

Wednesday October 1st

14:00-17:15	REGISTRATION
17:15-18:30	WELCOME and OPENING LECTURE John Hildebrand Explorations of a 'simple' olfactory system Host: Juan Bacigalupo
18:30-20:30	ROUND TABLE Ciencia, Sociedad y Política Chair: Adrián Palacios
20:30	WELCOME COCKTAIL

Thursday October 2nd

9:00-11:00	Symposium 1: Computational Neuroscience: vision, cold and more Chair: Patricio Orio Symposium 2: Mechanisms of memory formation and their alterations Chairs: Francisco Aboitiz, Pablo Fuentealba
11:00-11:30	Coffee break
11:30-12:30	PLENARY LECTURE: Alain Marty Deciphering synaptic signaling at single site level Host: Alan Neely
12:30-14:30	LUNCH
14:30-16:30	SPECIAL YOUNG NEUROSCIENTISTS SYMPOSIUM Chair: Juan Bacigalupo
16:30-18:30	Coffee and Posters I
18:30-19:30	PLENARY LECTURE Edward Tehovnik Myth and reality behind AVATAR: brain-machine interfaces Host: Jorge Mpodozis

Friday October 3rd

9:00-11:00	Symposium 3: The avian brain from a broad and comparative perspective Chairs: Gonzalo Marín Symposium 4: Channels and transporters as key modulators of neuronal excitability Chairs: Patricio Rojas, Magdalena Sanhueza
11:00-11:30	Coffee break
11:30-12:30	PLENARY LECTURE, Isabel Llano Imaging cerebellar activity in vivo with genetically-encoded calcium-dependent proteins Host: Magdalena Sanhueza
12:30-14:30	LUNCH
14:30-16:30	Oral presentations I and II
16:30-18:30	Coffee break and Posters II
18:30-19:30	SCN AWARD LECTURE, Luis Robles Auditory perception: cochlear mechanisms and modulation by attentional processes Host: Paul Délano
19:30-20:15	ASAMBLEA DE SOCIOS
21:00	DINNER

Saturday October 4th

9:00-11:00	Symposium 5: Exploration of brain dynamics and human cognition by intracranial EEG Chair: Tomás Ossandón Symposium 6: Genetics and development of the nervous system Chair: Kate Whitlock
11:00-11:15	Closing Remarks



Plenary Lectures

EXPLORATIONS OF A “SIMPLE” OLFACTORY SYSTEM

Hildebrand, J¹., ¹Department of Neuroscience, College of Science, University of Arizona.

A long and productive tradition of comparative research on the nervous systems of invertebrates has contributed greatly to our understanding of the functional organization, development, and evolution of nervous systems in general and of neural mechanisms underlying behavior. Insects in particular offer powerful experimental model systems. The insects are remarkably speciose, diverse, and successful animals from which we can learn much about the evolution, mechanisms, and disorders of neural systems and behavior. Explorations of the diminutive brains of insects reveal principles and mechanisms of neural development and function and at the same time help us understand both beneficial and harmful insect behaviors. We analyze the neurobiological mechanisms through which information about behaviorally significant olfactory stimuli is encoded, processed, and integrated in insect brains and specifically how olfactory information ultimately initiates and controls natural behaviors. This presentation will focus on studies of the olfactory system of the giant sphinx moth *Manduca sexta*, dealing mainly with the antennal lobes (ALs), the primary olfactory centers in the brain. We seek to understand how primary-sensory inputs from olfactory receptor cells are processed in AL glomeruli and represented in their outputs and how those outputs are further processed down-stream in the brain. Insights from the moth's sex-pheromonal communication system led to recent analysis of olfaction-dependent interactions with host plants. A multidisciplinary approach combining chemical characterization of floral scent, behavioral experiments in a laboratory wind tunnel, and electrophysiology has enabled us to determine how mixtures of volatiles, at natural concentrations, control flight and feeding behaviors and are encoded in the ALs. Evidence points to coincident firing of glomerular output neurons as a mechanism for neural coding of the context or significance of an odor. Gas chromatography coupled with multi-channel CNS recording has enabled identification, in complex floral mixtures, of key odorants to which AL neurons are particularly responsive. Mixtures containing only a few of those floral volatiles are as effective as the complete, natural floral mixture in modulating flight.



DECIPHERING SYNAPTIC SIGNALING AT SINGLE SITE LEVEL

Marty, A¹, ¹Laboratory of Cerebral Physiology CNRS.

Most studies on the functional properties of central synapses use experimental data gathered from a large number of synaptic sites, which have potentially different properties. In recent years we have developed new methods to study synaptic function in single synaptic sites. We have focused our studies on single depressing GABAergic synapses where multivesicular release and postsynaptic receptor saturation have been documented. In a first approach, we have stimulated local vesicular release by eliciting calcium uncaging in single presynaptic terminals, and analysing the postsynaptic current responses. This approach suggested that single terminals vary in their ability to release vesicles: some terminals can release more vesicles than others, presumably because they have a larger number of vesicular docking sites. In a second approach, we have used paired recordings which entail single synaptic sites. We used failure/success patterns to estimate the number of vesicular docking sites, which varied from 1 to 6 among synapses. Variations of docking site numbers account for differences in release probability, as well as in the amplitude and decay kinetics of unitary postsynaptic currents. Upon repetitive stimulation, decreasing docking site occupancy likewise accounts for changes both in pre- and postsynaptic parameters. The results suggest that differences in docking site numbers determine intersynaptic variability, and that docking site occupancy is a key parameter controlling changes in single synapse signaling.



MYTH AND REALITY BEHIND AVATAR: BRAIN-MACHINE INTERFACES.

Tehovnik, E¹., ¹Brain Insitute, CNPq Investigator, University of Rio Grande do Norte, Natal, RN, Brazil.
(Sponsored by CNPq (National Council For Scientific And Technological Development Of Brazil, #300690/2012-6))

Brain machine interfaces (BMI) have become important in systems neuroscience with the goal to restore motor function to paralyzed patients. We assess the current ability of BMI devices to move objects. The topics discussed include: (1) the bits of information generated by a BMI signal, (2) the limitations of including more neurons for generating a BMI signal, (3) the superiority of a BMI signal using single cells versus electro-encephalography (EEG), (4) plasticity and BMI, (5) the selection of a neural code for generating BMI, (6) the suppression of body movements during BMI, and (7) the role of vision in BMI. We conclude that further research on understanding how the brain generates movement is necessary before BMI can become a reasonable option for paralyzed patients.



IMAGING CEREBELLAR ACTIVITY *IN VIVO* WITH GENETICALLY-ENCODED CALCIUM-DEPENDENT PROTEINS

G. Astorga, J. Bao, A. Jalil, J. Bradley and **Llano I.**

I will present recent experiments from our laboratory geared to functional studies of molecular layer interneurons (MLIs) of the murine cerebellar cortex *in vivo*. MLIs are GABA-releasing interneurons which control the firing pattern of Purkinje cells, the principal neurons of the cerebellar cortex, and form also a local interconnected network. We take advantage of the Cre-Lox system to selectively direct the expression of genetically encoded calcium sensors of the GCaMP family to MLIs by stereotaxic injections of floxed adeno associated viral vectors in mice expressing the Cre recombinase under the endogenous parvalbumin promoter (PV-Cre). 3-4 weeks after injection imaging MLIs *in vivo* is performed using a home-made 2-photon laser scanning system optimized for deep tissue imaging. I will describe the temporal and spatial profile of the activity dependent signals elicited in MLIs by activation of the parallel fiber system, which constitutes one of the main excitatory inputs to the cerebellar cortex. I will also discuss pharmacological studies allowing us to identify the different types of ligand-gated receptors which govern the PF-MLI synapses. I will also present recent studies in behaving mice which indicates that MLIs are strongly activated during performance of a rhythmic motor task.



AUDITORY PERCEPTION: COCHLEAR MECHANISMS AND MODULATION BY ATTENTIONAL PROCESSES

Robles, L. ¹Programa de Fisiología Y Biofísica, ICBM, Facultad de Medicina, Universidad De Chile. (Sponsored by Funded By Fondecyt 1080227 And 1120256)

In the last 40 years our previous understanding of cochlear physiology has experienced a remarkable change. The cochlea, from being a passive receptor having fairly broad frequency-tuned responses to sound, has become a sharply frequency-tuned and exceptionally sensitive receptor that adjusts its sensitivity according to the stimulus intensity. This significant change has been the result of new findings in cochlear mechanics and hair-cell physiology. The cochlea has two types of highly specialized receptor cells, inner and outer hair cells. Highly frequency-tuned cochlear vibrations produce displacements of hair-cell stereocilia, transducing mechanical vibrations into changes of hair-cell-membrane electrical potentials. These receptor potentials in inner hair-cells activate synapses with afferent neurons, originating action potentials that through afferent neural pathways reach the central nervous system. Prestin, a transmembrane protein present in outer hair cells, produces a voltage-dependent electromotile effect that generates cochlear amplification by boosting vibrations at each cochlear location. In addition to afferent pathways, the auditory system has conspicuous efferent pathways that project from the central nervous structures to the periphery, reaching as far as outer hair cells and afferent nerve fibers of the cochlea. These efferent fibers acting on outer hair cells modify the incoming sensory information traveling from the cochlea to the central auditory system. We have shown in chinchillas performing a visual discrimination task that selective attention to visual stimuli, through efferent-system activation, reduces cochlear neural responses. I will review the contributions of our group to the present knowledge of cochlear physiology, specifically on cochlear amplification and frequency tuning and on the role of the efferent system in the control of cochlear responses.



SYMPOSIUM

COMPUTATIONAL NEUROSCIENCE: VISION, COLD AND MORE

Chair: Patricio Orio

FROM COLD CURRENTS TO COLD RECEPTOR ACTIVITY PATTERNS: A COMPUTATIONAL STUDY BASED ON EXPERIMENTAL DATA

Braun, Hans¹, ¹Physiology, Medicine, Philipps University of Marburg. (Sponsored by Supported By Biomedizin & Technik (BM&T), Heidelberg-Marburg.)

Recordings of ion currents from cold and menthol sensitive ion channels provided new insight into ionic mechanisms of cold transduction. However, these data were obtained from isolated neurons' cell bodies and show essential differences compared to previous extracellular recordings of action potentials from cold afferent fibres. The latter are generated at tiny sensory nerve endings located in the superficial layers of the skin. Using a computer modeling approach, we can demonstrate that one of the major differences, the lack of spontaneous activity in neurons soma, can be attributed to those anatomical properties which make the neurons' soma accessible to recordings of membrane potentials and ion currents: their bigger size. Due to the larger membrane area of the neurons' soma, it can be expected that the physiologically relevant ion channels for temperature transduction appear in lower density as if they would be embedded in the tiny nerve endings. In contrast, the whole cell leak conductance and especially the membrane capacitance should almost proportionally increase with the membrane area. Such assumptions cannot be proven experimentally but can be checked by computer simulations. Indeed, increasing the membrane capacitance and leak conductance in a cold receptor model diminishes spontaneous activity while transient responses can still be elicited, exactly reflecting the experimental data. The model can also account for the experimentally observed induction of spontaneous activity in the soma by application 4-AP. Experimental impulse recordings from peripheral afferents and modeling strategies will be demonstrated by means of the "Virtual-Physiology" teaching tools "SimSkinsenses" and "SimNeuron" (www.virtual-physiology.com).



DIFFERENT ION CHANNELS INVOLVED IN COLD TRANSDUCTION: HOW DO WE PUT THEM TOGETHER?

Orio, Patricio¹, Olivares, Erick¹, Herrera, Gaspar¹, Madrid, Rodolfo², ¹Centro Interdisciplinario de Neurociencia de Valparaíso, Facultad de Ciencias, Universidad De Valparaíso. ²Departamento de Biología, Facultad de Química y Biología, Universidad De Santiago De Chile. (Sponsored by Fondecyt 1130862, Fondecyt 1131064, ACT-1113, ACT-1104 (Conicyt). ICM P09-022-F (Ministerio De Economía))

Since the cloning of the cold- and menthol-activated channel TRPM8, this channel has been identified as the principal responsible for the sensory transduction of innocuous cold. However, older and newer evidence has shown that cold transduction involves many other proteins as well. The electrical activity of cold-sensitive nerve endings and fibers shows in many species a variety of firing patterns -ranging from irregular tonic to regular bursting- depending on the temperature. These ongoing periodic patterns depend on TTX-R sodium channels, hyperpolarization-activated (HCN) channels and calcium-dependent mechanisms. The threshold for the response to temperature dynamically depends on the balance between TRPM8 and Kv1.2/1.2 channels. Also, temperature affects the kinetics and behavior of all channels and proteins. Due to the lack of electrical access to nerve endings, most of the molecular evidence comes from cultured cold-sensitive neurons which is supposed to resemble phenomena occurring at nerve endings. In order to link the evidence from cultured neurons to nerve endings behavior, we have been working in mathematical models of cold receptors that reproduce different aspects of cold receptors behavior. Our models have shown 1) why HCN1 channel kinetics is crucial for the correct timing of regular ongoing activity of cold receptors, 2) that Calcium-dependent desensitization of TRPM8 current is sufficient to explain the dynamical response of cold receptors to temperature changes, and 3) that experimental results linking the expression levels of TRPM8 and Kv channels to the response threshold can be extrapolated to nerve endings.



SPEED PROCESSING IN THE PRIMATE VISUAL SYSTEM

Masson, Guillaume¹, MESO, Andrew¹, ¹Institut de Neurosciences de la Timone, Medical School, CNRS & Aix-Marseille Université. (Sponsored by This Work Is Supported By CNRS, The French Agence Nationale De La Recherche (project SPEED, ANR-SHS2-2013) And The European Union (FET, BrainScales))

Measuring object motion speed is a critical information for controlling our actions. Still, we understand very little how speed information is reconstructed from the local changes in luminance generated by the image translation. One approach is to dissect out how spatiotemporal changes in luminance patterns are extracted at multiple scales and nonlinearly integrated. We have recently developed a new set of naturalistic textures, called motion clouds, that allow to probe these mechanisms (Sanz-Léon et al., J Neurophysiol, 2012). We will present new behavioral data showing how the primate visual system adaptively integrates these local information to control tracking eye movements. We will shown that the statistics of naturalistic stimuli help to improve accuracy and reliability of speed coding (Simoncini et al., Nature Neurosci, 2012). We will discuss these behavioral data in regards of the current knowledge of neural representation of speed information in non-human primate extrastriate cortical areas.



MOTION AND SPEED PROCESSING IN THE RETINA

Escobar, María-José¹, ¹Departamento de Electrónica Universidad Técnica Federico Santa María.

In the mammalian retina, around 20 types of retinal ganglion cells have been morphologically recognized, together with, functional circuitries sensitive to a different feature of the visual input. It has been also shown that the receptive fields of each retinal ganglion cell type cover the entire visual field independently with a few overlap between neurons of the same type. In other words, retina performs a parallel processing of different visual features at the same time. In the last few years a special emphasis has been put on the so-called non-standard ganglion cells, which are sensitive to complex features classically attributed to visual cortex. Most of the non-standard retinal ganglion cells respond to motion features, such as, motion direction, differential motion, approaching motion and texture motion. Ganglion cells processing these motion features are considered as non-standard retinal ganglion cells and their information is normally not considered in the current paradigm of motion processing in the dorsal stream. Along this talk we will review the main characteristics of these ganglion cell populations, and also, from *in-vitro* micro-electrode-array recording data, sniff around the potential speed coding in the retina.



SYMPOSIUM

MECHANISMS OF MEMORY FORMATION AND THEIR ALTERATIONS

Chairs: Francisco Aboitiz, Pablo Fuentealba

THE MEMORY OF MOTOR LEARNING: THE WHOLE IS MORE THAN THE SUM OF ITS PARTS.

Maldonado, Pedro¹., Mariman, Juan¹., Burgos, Pablo¹., ¹PDFB, BNI y CENEM, Facultad de Medicina, Universidad De Chile. (Sponsored by Supported By ICM P09-015F, ICM P10-001-F, And The Guillermo Puelma Foundation.)

It has been shown that the nervous system shows the ability to learn motor components of a task and then integrate these components in a unified manner. We conjectured that learning of new sensory-motor internal models explains this phenomenon and as well as the refinement in sensory-motor networks that occur when we practice. We examined the time course of phase synchronization in electroencephalographic signals (EEG) and the visuomotor coordination in both the composition condition (part) and the condition of decomposition (integrated) during a motor learning of a continuous task with kinematics and kinetics adaptations. We found that Learning was significant in both groups. After 5 days of practice, the “integrated” group showed reduced performance in kinetic task alone, and the “part” group had reduce performance in the kinematic component of the “integrated” task. We found little changes in phase synchronization among fronto-parietal electrodes between day 1 and day 5, for all subjects in alpha and beta bands. We also found that the behavior of visuomotor anticipation increased with practice in both groups, especially in the “integrated” group. Our results demonstrate that learning by “parts” are not readily transferred to a “integrated” task and vice versa, suggesting complex interaction of these mechanisms.



VISUAL AREAS EXERT FEEDFORWARD AND FEEDBACK INFLUENCES THROUGH DISTINCT FREQUENCY CHANNELS

Bosman, Conrado¹, ¹Swammerdam Institute for Life Sciences, Faculty of Science, University of Amsterdam.

Visual cortical areas are thought to form a hierarchy and to subserve cognitive functions by interacting in both feedforward and feedback directions. While feedforward influences convey sensory signals, feedback influences modulate brain responses to a given sensory stimulus according to the current behavioural context. Many studies have demonstrated effects of feedback influences on feedforward driven responses and on behaviour and anatomical projections in both directions have been identified. However, the neurophysiological mechanisms through which these influences are exerted remain largely elusive. Here we show that in the primate visual system, feedforward influences are carried by theta- band (~4 Hz) and gamma-band (~60-80 Hz) synchronization, and feedback influences by beta-band (~14-18Hz) synchronization. These frequency-specific asymmetries in directed influences were revealed by simultaneous local field potential recordings from eight visual areas and an analysis of Granger-causal influences across all 28 pairs of areas. The asymmetries in directed influences correlated directly with asymmetries in anatomy and enabled us to build a visual cortical hierarchy from the influence asymmetries alone. Across different task periods, most areas stayed at their hierarchical position, whereas particularly frontal areas moved dynamically. Our results demonstrate that feedforward and feedback signalling use different frequency channels, which might subserve their differential communication requirements and lead to differential local consequences. The possibility to infer hierarchical relationships through functional data alone might make it possible to derive a cortical hierarchy in the living human brain.



CORTICAL OSCILLATIONS DURING SOCIAL DECISION-MAKING USING GAME THEORY PARADIGMS

Billeke, Pablo¹, Zamorano, Francisco¹, Aboitiz, Francisco², ¹Centro de Investigación en Complejidad Social, Facultad de Gobierno, Universidad Del Desarrollo. ²Lab. Neurociencias Cognitivas, Facultad de Medicina, Pontificia Universidad Católica De Chile. (Sponsored by CONICYT [791220014], Project Anillo En Complejidad Social [SOC-1101] And By The Millennium Center For The Neuroscience Of Memory [NC10-001-F])

Experimentaleconomics has shown that humans do not behave following the classical rule of maximizing their own payoff. Several studies, using ultimatum game for instance, have demonstrated that other factors are also relevant to make social decision, namely inequity aversion, intention perception and moral attitude, among others. Interestingly, these studies show that brain regions related to emotional and rational processes are involved during social decision. In this presentation, I will show electrophysiological studies performed by our group. In these experiments we assessed the correlation between oscillatory brain activity and social decision making during bargaining. Our results suggest that Theta-band activity is related to the prediction errors in frontal brain regions. Furthermore, prediction errors seem to be higher during a social-context than during a non-social-context. Finally, we show that power and phase synchrony on the Alpha-band activity is related to the anticipation to other person's behaviors; this effect is found in the temporal and parietal regions. Thus, our results suggest that oscillatory brain activity in these regions underlies the behavioral adaptation during social interactions.



BRAIN HISTAMINE AND HIPPOCAMPAL NEURONAL DYNAMICS DURING LEARNING AND MEMORY.

Valdes, Jose¹., ¹Programa de Fisiologia y Biofisica, Medicina, Universidad de Chile. (Sponsored by Funded By: ICM-P10-001F CENEM.)

During spatial memory process, some critical neural networks phenomena emerge from the activity of principal hippocampal cells. The neural representation of the space is coded by the concerted activity of place cells generating a spatial or cognitive map. The activity of these place cells is very stable on time, if the sensory element of the environment state unchanged. However, if the sensory cues change the activity of the place cells may change in position, frequency or simply appear and disappear (remapping). In addition at the level of local field potential, a prominent theta oscillation appears in the hippocampus when the animal navigates. All those neural network phenomena: stability, remapping and theta oscillation, are necessary for the correct unfolding of learning and memory process. The idea that neuromodulatory system such as histamine may affect these hippocampal networks properties is poor understood. By combining pharmacological blocking of histamine receptor, behavior and high density electrophysiological recording, we demonstrate that the blocking of H1 receptor disrupt the place field stability, decrease the remapping capacity, disrupt the theta oscillations and impair the learning capacities of the rats. These results indicate a relevant role of histamine during learning and memory process.



SPECIAL YOUNG NEUROSCIENTISTS SYMPOSIUM

Chair: Juan Bacigalupo

NEGATIVE REGULATORS FOR MEMORY FORMATION AND REPROCESSING AFTER RETRIEVAL

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Animals are surrounded by a large number of diverse and changing stimuli. However, animals do not remember every perceived stimulus, nor make associations between all the stimuli around them. In that sense, there must be cellular and molecular mechanisms that constrain memory formation. Protein phosphatases are important regulators of neural plasticity and memory. Some studies support that the Ca²⁺/calmodulin-dependent phosphatase calcineurin (CaN) is a negative regulator of memory formation, although the signaling mechanisms by which CaN exerts its action in such processes are not well understood. The aim of this work was to study the role of CaN in contextual fear memory consolidation and reconsolidation in the hippocampus. We investigated the CaN control on the NF- κ B signaling pathway, a key mechanism that regulates gene expression in memory processes. Post-training intra-hippocampal administration of the CaN inhibitor FK506 enhanced memory retention one day but not two weeks after training. Moreover, the inhibition of CaN by FK506 increased NF- κ B activity in dorsal hippocampus. The administration of the NF- κ B signaling pathway inhibitor sulfasalazine impeded the enhancing effect of FK506. In line with our findings in consolidation, FK506 administration before memory reactivation enhanced memory reconsolidation when tested one day after re-exposure to the training context and also two weeks after training. The co-administration of sulfasalazine and FK506 blocked the enhancement effect in reconsolidation, suggesting that this facilitation is also dependent on the NF- κ B pathway. Our results support a novel mechanism by which memory formation and reprocessing can be controlled by CaN regulation on NF- κ B activity.



SIMULTANEOUS RECORDING OF LEFT AND RIGHT HIPPOCAMPUS DURING SLOW-WAVE SLEEP

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Multi-neuron recording from live animals has become one of the most used techniques to study the neurophysiological basis of cognitive processes. Memory consolidation is thought to be mediated not by a single, isolated brain structure but by multiple, interconnected brain areas. The hippocampus has been accepted as the main structure leading to acquisition and consolidation of newly memory traces. The hippocampus comprises two homologous structures located on each brain hemispheres. Despite the overwhelming amount of studies supporting the role of hippocampus in memory little is known whether it works as a whole interconnected structure or not. Studies in humans and mouse models have documented right-hemisphere dominance suggesting that hippocampal spatial memory functions may be lateralized. The current work presents a modified recording device capable of obtaining high-density recordings from both hippocampi simultaneously allowing us to investigate coherence/synchrony of extracellular signals between right and left hippocampus. We successfully recorded LFPs and hippocampal spikes from both hippocampi, as revealed by histological examination. Analysis of simultaneously recorded EEG during slow-wave sleep (SWS) showed a despaired degree of synchrony between LFPs. During SWS, lower frequency brain waves showed a higher degree of correlation than higher frequency brain waves (SWR, sharp-wave ripples). Within the SWR frequency spectrum (100-250Hz), we also observed variances in the coherence of events between both left and right hippocampus. We focused on sharp-wave ripples events since they are known to be mostly present during SWS and to be relevant for the memory consolidation process carried out by the hippocampus.



NA⁺-DEPENDENT GLUTAMATE TRANSPORTERS AS SIGNAL TRANSDUCTION MOLECULES IN GLIAL CELLS

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Glutamate the main excitatory neurotransmitter activates a wide variety of signal transduction pathways, which regulates the protein repertoire. Activity- dependent glutamate effects are assumed to be mediated through glutamate receptors however; recent findings suggest that the Na⁺-dependent glutamate transporters also known as excitatory amino acid transporters (EAATs), also participate in glutamate-induced signaling. To elucidate the role of EAATs as signal molecules, we use two models of radial glial cells, Bergmann glial cells (BGC) from cerebellum and Müller glial cells (MGC) from retina. BGC and MGC are in close proximity to glutamatergic synapses and participate in the recycling of glutamate. In this context, we demonstrated that EAATs activate downstream targets that increase i[Ca²⁺] concentrations, and regulate translation through the PI3K/Akt/mTOR pathway and transcription through the CaMKII/RSK/CREB pathway. In order to evaluate if this event was exclusive of radial glial cells, we decided to evaluate EAATs dependent-signaling in another kind of macroglia: oligodendrocytes. The primary culture of these cells is an excellent model to challenge this concept, since glutamate is involved in the biology of the myelinating cells of the CNS. In these cells we were able to demonstrate that EAATs regulate oligodendrocytes morphology through an increase of i[Ca²⁺] that triggers CaMKII α activation and actin cytoskeleton remodeling. Our results add new mediators of glutamate signaling that regulate cell morphology as well as gene expression at translational and transcriptional levels. Our findings strengthen the critical role of glial cells in the synaptic function.



HINDSIGHT REGULATES PHOTORECEPTOR AXON TARGETING THROUGH TRANSCRIPTIONAL CONTROL OF *JITTERBUG/FILAMIN* AND MULTIPLE GENES INVOLVED IN AXON GUIDANCE IN *DROSOPHILA*

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During axon targeting, a stereotyped pattern of connectivity is achieved by the integration of intrinsic genetic programs and the response to extrinsic long and short-range directional cues. How this coordination occurs is the subject of intense study. Transcription factors play a central role due to their ability to regulate the expression of multiple genes required to sense and respond to these cues during development. Here we show that the transcription factor HNT regulates layer-specific photoreceptor axon targeting in *Drosophila* through transcriptional control of *jbug/Filamin* and multiple genes involved in axon guidance and cytoskeleton organization.

Using a microarray analysis we identified 235 genes whose expression levels were changed by HNT overexpression in the eye primordia. We analyzed nine candidate genes involved in cytoskeleton regulation and axon guidance, six of which displayed significantly altered gene expression levels in *hnt* mutant retinas. Functional analysis confirmed the role of *otk/PTK7* in photoreceptor axon targeting and uncovered Tiggrin, an integrin ligand, and *Jbug/Filamin*, a conserved actin binding protein, as new factors required for layer-specific photoreceptor axon targeting. Moreover, genetic analysis showed that HNT acts partially through *Jbug/Filamin* *in vivo* to regulate axon guidance. Finally, we provided *in silico* and molecular evidence that indicates that *jbug/Filamin* is a direct transcriptional target of HNT.

Our work sheds light into the understanding of how transcription factors coordinate diverse cellular and molecular processes in order to achieve the correct connectivity pattern in the nervous system.



THE AVIAN BRAIN FROM A BROAD AND COMPARATIVE PERSPECTIVE

Chair: Gonzalo Marín

BIRDS DO HAVE A BRAIN: COLUMNS AND LAYERS IN THE AVIAN PALLIUM

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The pallial telencephalon is the most variable and diverse region of the amniote brain, among and within classes. In mammals this region is organized as a multi-layered cortex, in which cells of the different layers are functionally connected by radially oriented processes, which form restricted connections between layers. Due to this intrinsic connectivity, neurons included in a columnar section radially oriented across the layers tend to have common physiological properties, and are regarded as forming operational modules. In contrast, the pallial region of non-mammalian amniotes seems very different from the cortex, as it does not appear to be laminar, and no functional modules or recurrent local circuits have been described in it. Instead, the avian pallial sensory areas have traditionally been considered as a necklace of linearly related nuclei, lacking of recurrent interactions between them. Several recent works, including ours, have re-examined in detail the organization of the avian sensory pallium using modern anatomical methods. In agreement with other studies, we have found that the visual collopallium is composed of three differentiated, highly interconnected layers: internal (thalamo-recipient), intermediate (efferent,) and external (associative). Interconnections between these layers were formed by dorso-ventrally oriented, discrete columnar bundles of axons which follow a precise topographic homotopic arrangement. These interconnections appear to form operational modules in which cells located in homotopic positions in each layer are synaptically linked by a local loop of recurrent axonal processes. We discuss these results in the context of the evolutive divergence between the sauropsid and mammalian pallial territories.



PRINCIPLES OF CEREBELLAR ORGANIZATION: WHAT WE HAVE LEARNED FROM BIRDS.

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The cerebellum is highly developed in both birds and mammals consisting of numerous transverse lobules or folia. More striking, the cerebellum is organized into sagittal zones which cut across the lobules. This sagittal organization can be seen with respect to afferent inputs, cerebellar Purkinje cell (PC) projections and the physiological responses of PCs. Furthermore, many molecular markers show a sagittal organization in the cerebellum, the most thoroughly studied of which is zebrin II (ZII). In both birds and mammals ZII is expressed such that there are sagittal stripes of PCs with high expression (ZII+) interdigitated with stripes of little or no expression (ZII-). However the significance of these ZII stripes has remained elusive. In this talk I will discuss what we have discovered in our studies of the cerebellum in birds. First, the pattern of ZII expression is highly conserved, as ZII stripes are present in a wide number of species including the basalpaleognaths and some squamate reptiles. Second, I will discuss the relationship of the ZII stripes to other molecular markers and afferent inputs to the cerebellum. Finally, I will highlight our work exploring the relationship of ZII expression to the response properties of PCs in the pigeon vestibulocerebellum. Vestibulocerebellar PCs respond to particular patterns of optic flow resulting from self-motion in 3-dimensional space. We have found that the PCs within a ZII+/- stripe pair all respond best to the same pattern of optic flow. That is, a ZII+/- stripe pair forms a functional unit in the cerebellum.



ECOLOGY, PHYLOGENY AND THE EVOLUTION OF THE AVIAN BRAIN

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The avian brain appears to be different in its anatomy from that of mammals, but it nevertheless supports a very similar diversity of behaviours and cognitive abilities. In recent years, it has become clear that this behavioural diversity in birds is related to diversification of the anatomy of the brain. For example, the amazing cognitive abilities of parrots are supported by an expansion of 'neocortical' regions in the brain that parallels that of non-human primates. Expansions in the size and morphology of brain regions is also associated with foraging behaviour. This includes a number of anatomical changes in visual and auditory regions in owls to enable stereoscopic vision and the ability to locate prey in complete darkness. Perhaps less well known are the evolution of differences in the trigeminal pathways of somatosensory specialists, such as waterfowl, sandpipers and the kiwi of New Zealand. Taken together, this wealth of data has provided a great deal of insight into the correlated evolution of brain and behaviour in birds. We can now use this information to better understand the sensory abilities of extremely rare and even extinct species, two examples of which will be discussed. This area of research is, however, still in its infancy. A great deal more information on species differences in brain anatomy, such as neuron size and numbers, will be needed if we are to understand general patterns of brain evolution and the processes underlying the behavioural and cognitive diversity of birds and other vertebrates.



THE AVIAN TECTOFOGAL SYSTEM, A PATHWAY FOR UNDERSTANDING VISION AND ATTENTION

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The tectofugal (collothalamic) pathway is the main visual pathway in most vertebrates. Its principal visual center, the optic tectum or superior colliculus, receives retinal afferents in its superficial layers and gives rise to several efferent pathways from deeper layers. In amniotes, the ascending tectofugal pathway originates in motion-sensitive tectal ganglion cells (TGCs), which send a massive projection to the nucleus rotundus (Rt) (birds and reptiles) or the caudal pulvinar (mammals) in the dorsal thalamus. Evidence indicates that in both pigeon and mouse, the input to the TGCs originates from the same retinal ganglion cell class, which in addition is the most numerous in the retina. Therefore, the TGCs seem to be a key component of a highly conserved visual pathway that transmits visual motion signals from the tectum to the pallium in all amniotes. In the present talk, it will be described the parallel organization of this pathway in pigeons, from the tectum to the final telencephalic target, the arcopallium, and from there back to the tectum. Evidence will be presented that this recursive anatomy allows that bottom-up and top-down signals interact in the tectum to select the retinal activity that flow and synchronize responses along this pathway, setting the stage for stimulus selection and attention. Finally it will be argued that, given that this pathway is remarkably conserved in birds and mammals, its elusive function would be much easily revealed by using results gathered in one group to guide the research of the missing evidence in the other.



CHANNELS AND TRANSPORTERS AS KEY MODULATORS OF NEURONAL EXCITABILITY.

Chairs: Patricio Rojas, Magdalena Sanhueza.

OXYSTEROLS AND NMDA RECEPTOR FUNCTION

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Oxysterols are cholesterol metabolites. The major oxysterol in brain is 24S-hydroxycholesterol (24S-HC). Although other functions for 24S-HC have been proposed, it is thought mainly to be a disposal vehicle for the labile neuronal pool of cholesterol. We have recently found that 24S-HC is a positive allosteric modulator of NMDA receptors, glutamate receptors involved in normal synaptic plasticity and in neuronal death and dysfunction. We also characterized two synthetic 24S-HC analogues with similar actions. These may find application in the treatment of neuropsychiatric disorders, such as schizophrenia, thought to involve NMDA receptor hypofunction. 24S-HC and its analogues exhibit a number of peculiar pharmacological properties. Onset and offset of action are very slow, possibly suggesting a non-aqueous site of action and membrane partitioning. In agreement with this, oxysterol is effective when applied indirectly, to the bath outside a cell-attached patch. With extracellular oxysterol application, potentiation is evident in excised outside-out patches, suggesting that neither soluble second messengers nor receptor insertion explains potentiation. Cytoplasmic application is ineffective in whole-cell recordings and in inside-out patches, so endogenous oxysterol actions likely require release from cells. Oxysterols accelerate block by the open-channel blocker MK-801, indicating that channel open probability is increased. Single-channel studies demonstrate that this increase arises mainly from an increase in the shortest open time component and a decrease in the longest closed time component, with no change in relative frequencies. Our results elucidate an important new class of neuromodulator and potential pharmacological intervention.



A MECHANISM FOR DYNAMIC MODULATION OF NEURONAL THETA FREQUENCY PREFERENCE IN INTERPLAY WITH NETWORK ACTIVITY

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Subthreshold theta-resonance is an intrinsic property of neurons from brain regions involved in memory, consisting of a selective responsiveness to stimuli of a preferential frequency (resonance frequency, F_{res}) in the 4-8Hz range. Subthreshold frequency preference may selectively translate incoming oscillatory inputs at F_{res} to spiking, contributing to orchestrate neuronal network rhythms. However, this is unclear because the decrease in neuronal input resistance (R_{in}) caused by synaptic bombardment in active circuits may dampen resonance. We conducted whole-cell recordings in rat brain slices to compare resonance and its ability to drive tuned firing in hippocampal CA1-pyramidal cells and olfactory amygdala neurons (displaying ~3-fold larger R_{in} in a silent network). We investigated sub and perithreshold frequency preference, mimicked synaptic noise in single cells with dynamic clamp and conducted computational simulations. While a hyperpolarization-activated cationic current (I_H) underlies subthreshold resonance in both groups, I_H effectively filters perithreshold voltages only in amygdala neurons due to their higher R_{in} , thus allowing frequency preference translation to spiking even in the active network state. In turn, the perithreshold preservation of frequency preference in hippocampal neurons depended on the relative levels of a muscarine-sensitive potassium current (I_M) and a persistent sodium current (I_{NaP}). The amplifying effect of I_{NaP} contributed to compensate for low R_{in} in these neurons. Remarkably, we showed that F_{res} was modulated by R_{in} changes generated by synaptic inputs. Therefore, different intrinsic mechanisms allow effective resonance expression in the spiking regime. In the intact brain frequency preference may be dynamically tuned in interplay with network activity levels.



NUTRIENT TRANSPORTERS FEEDING STARVING SYNAPSES.

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The brain makes up 2% of a person's weight. Despite this, even at rest, the brain consumes 25% of the body's energy. Most of the energy consumed in the brain is attributable to restoration of the membrane gradient following neuronal depolarization. Neurotransmitter recycling, intracellular signaling and dendritic and axonal transport also require energy. Even though neurons are responsible for massive energy consumption, the brain is made up of many cells, including neurons, glial and ependymal cells. Every brain cell has a specific function and thus every brain cell has different metabolic needs. Many of these specific functions are concerned with maintenance of neuronal transmission. Astrocytes play a central role in supporting neurons metabolically by producing lactate, through glycolysis and activation of glycogen catabolism. There have been several reports of metabolic impairment in a variety of neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and Parkinson's disease, among others. Moreover, deregulation of energy metabolism could be implicated in an increased production of oxidative species. During the last 10 years we have been making steady progress in the mechanisms of communication between neurons and glial cells, the way they regulate their metabolism, and the use of ascorbic acid as inter cellular messenger. Here, we will describe the regulation of neuronal glucose, lactate and ascorbic acid transporters under synaptic activity in mice models of Huntington's disease. Experiments demonstrating a failure in ascorbic acid-dependent modulation on neuronal metabolism in Huntington's disease will be discussed. Brain is an expensive organ in energetic terms so disruptions in energy production may affect neuronal transmission and thus, neuronal survival. FONDECYT1110571, DID-UACH.



CHLORIDE CO-TRANSPORTERS IN NEUROPSYCHIATRIC DISORDERS

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GABA is the main inhibitory neurotransmitter in the nervous system, which opens Cl⁻ selective channels. Depending on the intracellular Cl⁻ concentration, the ion flux could cause either inhibitory or excitatory effects. In immature neurons elevated Cl⁻ is due to the action of Na⁺ K⁺ Cl⁻ co- transporter 1 (NKCC1), which is observed in some types of epilepsy, causing that antiepileptic drugs do not decrease excitability, and in some cases increase seizure frequency. Recent evidence suggest that in schizophrenia, a disorder in which there is also a decrease in inhibition, there is an increase in the ratio of NKCC1/KCC2 messenger. In order to study how chloride co-transporters and Cl⁻ levels are involved in circuit remodeling in these neuropsychiatric conditions, we study the role of NKCC1 by using behavioral, biochemical and electrophysiological techniques. In dentate gyrus of adult rats with chronic epilepsy the NKCC1-dependent component of GABAergic synaptic response is increased with respect to controls, suggesting that this co-transporter is more express in comparison to mature adults. Application of the specific NKCC1 blocker Bumetanide decrease the global circuit excitability in epileptic animals returning it to values close to control. This evidence shows that in epileptic conditions the increased excitability is produced not only by loss of GABAergic interneurons, but also by altering the Cl⁻ driving force. In other hand, schizophrenic-like animals showed an increase in excitability of CA3-CA1 and perforant path-Dentate Gyrus synapses, but only the last one exhibit changes when NKCC1 was blocked, showing that alterations in this co-transporter are localized in the hippocampal circuit. Taken together, these results suggest that chloride homeostasis is an important physiological target to be study in terms of understanding neuro-psychiatric diseases, and might be one of the links accounting for the co-morbidity observed in patients.



EXPLORATION OF BRAIN DYNAMICS AND HUMAN COGNITION BY INTRACRANIAL EEG

Chair: Tomás Ossandón

CONSCIENCE, INTRACRANIAL RECORDINGS AND CLINICAL APPLICATIONS

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Understanding levels of consciousness and the transitions between conscious and unconscious states has important theoretical and clinical implications. Yet despite the fact that we typically enter a state of unconsciousness every night, remarkably little is known about how we fall asleep or lose consciousness while getting sedated. In a series of hd-EEG and intracranial experiments of people falling asleep or getting sedated with propofol, we explored the limits of perceptual and semantic decisions, inhibitory control, top-down and bottom-up target detection and introspection. We found there is a differential modulation of the cognitive control capacities by wakefulness. In the transition to unconsciousness, drowsiness affects inhibitory control and top-down target detection earlier than perceptual and abstract (semantic) decisions. We can take decisions, learn, perceive when losing consciousness and even when unconscious, but these are different. Clinical implications are discussed in this light. We believe these results may help to link experimentally a handful of theoretical frameworks giving rise to a more parsimonious explanation of what makes us human.



TOWARDS AN ECOLOGICAL NEUROSCIENCE: NATURAL VISION, LANGUAGE AND IMAGINATION.

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In cognitive neuroscience, protocols of increasing complexity are used to mirror natural conditions and behavior. These are likely to recruit complex and intertwined neurophysiological and cognitive processes. In this context, I focus my research on brain dynamics involved in two very conspicuous and natural human behaviors: active visual exploration and language processing. I profit from the high spatial and temporal resolution of intracranial-EEG (iEEG) recordings to measure brain activity in protocols that require active vision or the unfolding of linguistic behavior. Spectral analyses of the recorded signals (particularly in the high-frequency range) provide precise estimates of when and where the brain becomes active during the task. Finally, the comparison of those brain dynamics with behavioral measures (such as reaction-times, eye movements, or spoken language) reveals the functional contribution of different brain networks. Here I would like to show three studies focusing on the functional organization of the ventral visual stream in canonical highly controlled conditions, natural vision and relatively spontaneous behavior. The results show that while some of the properties of the system are highly preserved as we move towards increasingly more natural conditions, novel phenomena and also novel questions arise. This confirms the need to develop protocols as close as possible to natural conditions (i.e. the use of more naturalistic stimuli and less behavioral restriction) in order to achieve a better description of brain dynamics and cognition.



CONTROL, TRAINING AND ALTERATIONS OF ATTENTION FROM A NOVEL VIEW

Ossandón, T¹., Jean-Philippe, Lachaux²,¹Department of Psychiatry , Medical School, Pontificia Universidad Católica De Chile.²INSERM-CNRS Université Lyon 1. (Sponsored by This Work Was Supported By The Millenium Center For The Neuroscience Of Memory, Chile, NC10-001-F, With Innovation For Competitivity Funds From The Ministry For Economics, Fomentation And Tourism, Chile, And Fondecyt 1140996)

The brain displays moment-to-moment activity fluctuations that reflect various levels of engagement with the outside world. Processing external stimuli is not only associated with increased brain metabolism but also with prominent deactivation in specific structures, collectively known as the default-mode network (DMN). The role of the DMN remains enigmatic partly because its electrophysiological correlates and temporal dynamics are still poorly understood. Using wide-spread depth recordings in epileptic patients, undergoing intracranial EEG during pre-surgical evaluation, we reveal that DMN neural populations display task-related suppressions of gamma (60-140 Hz) power and, critically, we show how millisecond temporal profile and amplitude of gamma deactivation tightly correlate with task demands and subject performance. The results show also that during an attentional task, sustained activations in the gamma band power are presented across large cortical networks, while transient activations are mostly specific to occipital and temporal regions. Our findings reveal a pivotal role for broadband gamma modulations in the interplay between activation and deactivation networks mediating efficient goal-directed behavior.



DIFFERENTIAL COGNITIVE STATE-DEPENDENT RECRUITMENT OF HIGH-FREQUENCY OSCILLATIONS IN THE HUMAN HIPPOCAMPUS

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Ripples are high-frequency bouts of coordinated hippocampal activity believed to be crucial for information transfer and memory formation. We used intracortical macroelectrodes to record neural activity in the human hippocampus of awake subjects undergoing surgical treatment for refractory epilepsy and distinguished two populations of ripple episodes based on their frequency. The phase-coupling of one population, slow ripples (90-110 Hz), to cortical delta oscillations was differentially modulated by cognitive state; whereas the second population, fast ripples (130-170 Hz), was not seemingly correlated to local neural activity. Furthermore, as cognitive demands increased, the ongoing coordination of neural activity induced by slow ripples progressively augmented along the parahippocampal axis. Thus, during quiet rest, slow ripples were locally organized in restricted hippocampal territories; whereas during attentionally-demanding states, slow ripples coordinately recruited the hippocampus and parahippocampal cortex, consistent with ripples supporting information transfer and synchronizing anatomically distant regions. Hence, our results provide further evidence of neural diversity in hippocampal high-frequency oscillations and their association to cognitive processing in humans.



GENETICS AND DEVELOPMENT OF THE NERVOUS SYSTEM

Chair: Kate Whitlock.

MAKING BRAINS: IN VIVO IMAGING ANALYSIS IN THE DEVELOPING ZEBRAFISH EMBRYO

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The development of vertebrate neuroepithelium with a well-organized apico-basal polarity and central lumen is critical for its proper function. However, how this apico-basal organization is established during embryonic development and what the contribution of surrounding signals and tissues that might influence such organization has remained largely unknown. Our lab is interested to uncover the cellular and molecular mechanisms that establish and shape the developing brain and spinal cord. We study these processes by combining the superior transparency and genetics of the zebrafish embryo as this allows to visualize and quantify *in vivo* the cellular and molecular dynamics that govern neural tube morphogenesis and apico-basal development. In this talk, I will discuss recent studies revealing how co-ordinated cell-cell interaction coupled with adjacent tissues dynamics are critical to regulate final neural tissue architecture. Furthermore, new findings show how the spatial regulation and timing of orientated cell division are key steps for defining proper ventricle lumen formation. Together, zebrafish neurulation not only offers fundamental insights to understand early vertebrate brain development but it also offers the possibility to explore *in vivo* cell and tissue dynamics during complex three-dimensional animal morphogenesis.

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GENETIC DISSECTION OF NEUROPEPTIDE-CONTROLLED SEQUENTIAL BEHAVIOR.

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The insect molt culminates with ecdysis, a vital behavior that is used to shed the remains of the old cuticle. Ecdysis includes several behavioral subroutines and physiological events that are expressed sequentially to loosen and then shed the old cuticle, then expand and harden the new one. Ecdysis is triggered by the neuropeptide, Ecdysis-Triggering Hormone (ETH), which activates sequentially a number of peptidergic neurons, all of which express the ETH receptor (ETHR), and include neurons that produce Eclosion Hormone, Crustacean Cardioactive Peptide (CCAP), and bursicon, amongst others.

To understand how the complex temporal pattern of neural activation that underlies ecdysis is controlled, we used the calcium sensitive GFP, GCaMP, to monitor the pattern of activation of peptidergic ETH targets when ETH action was decreased by driving ETHR RNAi expression, and when neuropeptides downstream of ETH were genetically eliminated. In addition to monitoring the behavior of the intact animal, we expressed GCaMP in motoneurons, which provided an in vitro readout of the resulting behavior.

We found that reducing ETH action caused the greatest impact on neural activity and ecdysis behavior when ETHR RNAi was targeted to CCAP neurons. In addition, we found that neuropeptides released by the targets of ETH themselves are critical for determining the responses to ETH. Finally, we found that GABA inhibition, primarily of CCAP neurons, is critical for delaying the activation of these neurons and of ecdysis behavior.

Our results reveal that the actions of neuropeptides downstream of ETH together with GABA-mediated inhibitory actions configure the network's response to ETH to control the ensuing sequence of behavioral subroutines. In addition to contributing to the further understanding of how ecdysis behavior is controlled, our results provide insights for understanding how neuropeptides can fundamentally alter the output of a neural network.



GENETICS OF SOCIAL BEHAVIOR IN DROSOPHILA

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How the brain processes social information and integrates it with other forms of perception and learning is one of the major new frontiers in neuroscience. Its genetic basis remains particularly inaccessible, presumably because of the subtlety of the phenotype and the pleiotropy of the genes likely to influence it. Two new approaches to this problem will be described, one making use of the variation in social behavior found among various species of *Drosophila*, and the other based a human genetic syndrome unusual both for the specificity of its effects on social behavior, and the definitiveness of its genetic etiology: Williams Syndrome. Using both approaches, we have begun to define networks of genes influencing social behavior.



THE OLFACTORY SENSORY SYSTEM DEVELOPS FROM COORDINATED MOVEMENTS WITHIN THE NEURAL PLATE

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Background: The peripheral olfactory sensory system arises from morphologically identifiable structures called placodes. Placodes are relatively late developing structures, evident only well after the initiation of somitogenesis. Placodes are generally described as being induced from the ectoderm suggesting that their development is separate from the coordinated cell movements generating the central nervous system.

Results: With the advent of modern techniques it is possible to follow development of the neurectoderm giving rise to the anterior neural tube, including the olfactory placodes. The cell movements giving rise to the optic cup are coordinated with those generating the olfactory placodes and adjacent telencephalon. The formation of the basal lamina separating the placode from the neural tubes is coincident with the anterior migration of cranial neural crest.

Conclusions: Olfactory placodes are transient morphological structures arising from a continuous sheet of neurectoderm that gives rise to the peripheral and central nervous system. This field of cells is specified at the end of gastrulation and not secondarily induced from ectoderm. The separation of olfactory placodes and telencephalon occurs through complex cell movements within the developing neural plate similar to that observed for the developing optic cup.

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ORAL PRESENTATIONS



ION CHANNELS, EXCITABILITY AND SYNAPSES

MECHANISMS OF CORTICAL INHIBITORY PLASTICITY IN FRAGILE X SYNDROME

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A prominent phenotype of Fragile-X Syndrome (FXS) patients is hypersensitivity to sensory stimuli, with most patients finding smooth surfaces to be irritating and sometimes painful to the touch, while others exhibiting sensory “defensiveness”. Thus, both somatic sensation and cognitive interpretation of somatic activity are clearly disrupted in this disorder making the somatosensory cortex a highly relevant brain region to study FXS. While alterations in excitatory synapse function and plasticity are well established in *Fmr1KO* mouse models, recent studies now identify prominent defects in cortical inhibitory neurotransmission. In this study, we hypothesize that inhibitory short and long term synaptic plasticity are disrupted by specific interneuron-drive dysfunction. To answer this hypothesis we performed whole-cell patch-clamp recordings on identified low threshold spiking (LTS) interneurons and pyramidal cells from control and the FXS mouse model. In these experiments we studied long term depression of the inhibition (LTDi), depolarization-induced suppression of the inhibition (DSI) and slow-self inhibition (SSI), three phenomena known to be mediated by interneurons. Our results show that pyramidal cells from the layer II/III of somatosensory cortex of control mice undergo LTDi when layer IV is stimulated at HFS. Also, pyramidal cells from control animals express DSI when cells were depolarized to 0mv for 5 seconds. In contrast, pyramidal cells from the *Fmr1KO* mice failed to elicit LTDi, and DSI was drastically reduced. In addition, we tested whether LTS interneurons elicited SSI, an auto-inhibitory mechanism that operates in response to high neuronal activity. When LTS interneurons of control mice were tested, SSI was induced by a protocol of high frequency action potential activity. However, in LTS interneurons from *Fmr1KOs*, SSI was completely abolished. These data indicate that the inhibitory drive of the somatosensory cortex is altered and suggest sensory hypersensitivity at least partially stems from alterations in interneuron function.



THE ROLE OF I_{KD} CURRENT IN PAINFUL HYPERSENSITIVITY TO COLD INDUCED BY CHRONIC PERIPHERAL NERVE INJURY

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Cold allodynia is a common form of neuropathic pain induced by axonal damage of primary somatosensory neurons. The cellular and molecular mechanisms underlying this often disabling sensory alteration are poorly understood. Cold-sensitivity of cold thermoreceptor neurons is determined by a balance between the excitatory TRPM8-dependent current and I_{KD} , a potassium current that acts as an excitability break. We studied the role of I_{KD} current in painful hypersensitivity to cold after nerve damage, using chronic constriction injury (CCI) of sciatic nerve as a model of axonal damage-induced cold allodynia in mice, in combination with calcium imaging and patch clamp recordings in cultured neurons from dorsal root ganglia. We found that the population of cold-sensitive neurons (CSNs) is increased after injury, and that the thermal threshold to cold stimuli in CSNs is shifted to higher temperatures. In addition, the mean I_{KD} current density is reduced in CSNs from CCI animals compared to sham mice, with no major differences in TRPM8-dependent current density. Consistently, mathematical modeling of a cold thermoreceptor shows that a reduction in I_{KD} current density shifts the thermal threshold to higher temperatures. The electrophysiological characterization of CSNs shows an increase in the population of neurons with nociceptive-like phenotype among neurons from injured animals. These results suggest a recruitment of nociceptive neurons due to the reduction of the functional expression of potassium channels responsible for I_{KD} , providing a mechanism for cold allodynia.



BIDIRECTIONAL MODULATION OF THERMAL AND CHEMICAL SENSITIVITY OF TRPM8 CHANNELS BY THE INITIAL REGION OF THE N-TERMINAL DOMAIN

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TRPM8, a calcium-permeable cation channel activated by cold, menthol, and voltage, is the main molecular entity responsible for detection of cold temperatures in the somatosensory system. The N-terminus of TRPM8 consists of 693 residues and little is known about its contribution to the function and regulation of this channel. We performed selective mutations within the N-terminal domain of TRPM8, assessing their activity using calcium imaging and patch clamp techniques in transfected HEK293 cells. We identified two different regions within this domain that contribute to the activity, proper folding and assembly of this channel. We found that the deletion or substitution of the first forty amino acids yield channels with higher responses to cold and menthol. Site-directed mutagenesis screening revealed that single point mutations of positions S26 or S27 by proline caused the same enhanced thermal and chemical sensitivity. Electrophysiological analysis revealed that the enhanced sensitivity to agonists is due to a shift in the voltage-dependence of activation, increasing the probability of channel openings at physiologically relevant membrane potentials. In addition, we found that the region encompassing positions 40 to 60 is a key element in the proper folding and assembly of TRPM8; different deletions and mutations within this region rendered channels with an impaired function that are retained in the endoplasmic reticulum. These results suggest an important contribution of the initial region of the N-terminus in the setting of the thermal and chemical sensitivity and the proper assembly of TRPM8.



ROLE OF BASAL FOREBRAIN CHOLINERGIC NEURONS IN OLFACTORY LEARNING

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The ability of the olfactory system to represent sensory cues is strongly influenced by neuromodulators released in response to a challenging and constantly changing external environment. Of particular interest is the neuromodulator acetylcholine (ACh), which has been linked in several brain regions with attention and cue detection. The olfactory bulb and piriform cortex receive abundant cholinergic innervation from the basal forebrain (BF) and it has been suggested that in these regions ACh is required to generate a more efficient olfactory coding, ultimately affecting olfactory learning and memory. How BF neurons are activated during active olfactory learning, however, remains unknown. Here, we performed electrophysiological recordings from the BF of awake and freely moving animals exposed to the associative learning paradigm go-no go. This task studies the capacity of a water-deprived rodent to actively discriminate between two odorants (a rewarded and a non-rewarded odor). To study the exclusive contribution of cholinergic release to olfactory learning at the end of the behavioral session we used selective optogenetic stimulation to identify cholinergic neurons of the BF. Specifically, we stereotactically inserted an optetrode (composed of an optical fiber and four tetrodes) into the BF of animals expressing channelrhodopsin (ChR) under the control of the choline acetyltransferase (ChAT) promoter, an enzyme that is exclusively expressed in cholinergic neurons. Cholinergic neuron identification was performed by applying blue light directly into this region and by performing off-line spike sorting analysis.



M-CHANNEL ACTIVATORS RESCUE HOMEOSTATIC REGULATION OF STRIATAL EXCITABILITY AND AMELIORATE LOCOMOTOR DEFICITS IN THE R6/2 HUNTINGTON'S MOUSE

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We describe a fast activity-dependent homeostatic (fADH) regulation of the intrinsic excitability of medium spiny neurons(MSN) in mouse dorsal striatum. fADH is progressive reduction in the number evoked impulses and increased variability in interspike interval. The properties of fADH are consistent with is due to a progressive recruitment of the M-current that is mediated by KCNQ2/3 channels. Three lines of evidence support this notion: 1) fADH is blocked by M-current antagonist XE991 (6 μ M), 2) whole cell voltage clamp recordings indicate that fADH induction increases the magnitude of an outward XE991 sensitive current, and 3) blocking PIP2 synthesis with 10 μ M Wortmannin reduces fADH. This homeostatic plasticity mechanism is significantly depressed in MSNs of the R6/2 transgenic mouse model of Huntington's Disease (HD). This deficit in fADH can be at least partially reversed *in vitro* by superfusion with KCNQ channel activators, such as 10 μ M retigabine. In vivo, R6/2 mice were treated with daily i.p. injections of retigabine (10mg/kg), for four weeks, starting at 4 weeks of age, and locomotor activity was assessed with the open field test in weeks 5-7. Activity levels in the treated HD mice were significantly improved. Thus, we suggest that a functional down regulation of the M-current contributes to a neuronal hyperactivity and network dysregulation that may lead to the neurodegeneration observed in these model systems, and that KCNQ2/3 channel regulation may be a target for therapeutic intervention.



Accessory subunit gamma1 modifies BK channel external architecture despite a minor effect on gating currents.

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Regulatory α and β subunits are responsible for conferring functional diversity to BK channels but little is known about the detailed way that accessory subunits modulate the structure the pore forming subunit. It is known that β 1 subunit produces a large leftward shift of the open probability vs. voltage curve in the absence of internal Ca^{2+} . Measuring gating currents, we observed that β 1 produce a subtle effect on voltage sensor activation. To explore the effect on the architecture of α subunit in the presence of β 1 subunit, we used lanthanide-based resonance energy transfer (LRET) as a molecular ruler to measure inter-molecular distances. We introduced a genetically encoded lanthanide binding tag (LBT) that binds Tb^{3+} (LRET donor) with high affinity at different positions in α and β 1 subunits. Fluorescent probe bodipy linked to a scorpion toxin, was used as LRET acceptor. We analyzed LRET sensitized emission (SE) decays using a nano-positioning system that determines the position of LBT-tagged sites with respect to the fixed acceptor near the pore axis. Interestingly, when the BK α subunit was co-expressed with the regulatory β 1 subunit, SE from α -LBT constructs different, indicating a conformational change of the voltage sensor domain of BK channel. In addition, β 1-LBT positions were found peripherally positioned to α subunit. Our results are the first evidences on the position of β 1 subunit in relation to α and the BK channel's external surface structure in the presence of the β 1 subunit.



ENVIRONMENTAL ENRICHMENT INCREASES RYR3 PROXIMAL PROMOTER METHYLATION AND AUGMENTS ITS TRANSCRIPTIONAL ACTIVITY.

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Ryanodine Receptors (RyRs) are intracellular calcium release channels, which through calcium-induced calcium release participate in long-term potentiation (LTP). Moreover, two of the three RyR isoforms, namely RyR2 and RyR3, have been involved in learning and memory processes. A recent report showed that the transcriptional activity of RyR2 and RyR3 increases in rat hippocampus after spatial memory training in the Morris water maze, prompting interest in understanding the mechanisms that underlie this transcriptional regulation, with particular interest on environmental-behavioral induced transcriptional activity. Here, we evaluated if RyR transcriptional activation occurs in mice exposed to an environmental enrichment paradigm. We found that mice exposure to an enriched environment increases the transcriptional activity of both, RyR2 and RyR3; moreover, we show that a change in methylation of the RyR3 proximal promoter is associated to the augmented transcriptional activity observed in response to the enriched environment. In order to understand how changes in methylation translate into increased transcriptional activity, we evaluated RyR3 mRNA levels in control and MeCP2-null mice. The reduced RyR3 mRNA levels displayed by MeCP2-null mice relative to controls, opens the interesting possibility that MeCP2 acts as a transcriptional activator of the RyR3 gene. The possible participation of MeCP2, together with the environment-induced changes in RyR3 promoter methylation, in directing RyR3 transcriptional activation has important implications for hippocampal LTP, learning and memory. Supported by the Biomedical Neuroscience Institute (BNI P-09-015F; Millennium Scientific Initiative), FONDECYT (1140162, 1140545), CECs is funded by the Centers of Excellence Base Financing Program of CONICYT.



MECHANISM OF THE PERMEATION PATHWAY IN HV1 CHANNEL

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Voltage-gated proton channels (Hv1) are integral membrane proteins with the capacity to permeate elementary particles in a voltage- and pH-dependent manner. Although Hv1 primary topology is known, lack of details regarding its structure in the open conformation has hindered the possibilities to find an adequate molecular model to account for the molecular determinants of their function and regulation (Pupo et al 2013). On the other hand, the discrepancy between the different Hv1 structural models proposed has limited the understanding of structure-function relationships and the finding of specific blockers for Hv1 (Pupo et al., 2014). Here, using non-stationary fluctuation analysis to determine the unitary conductance, and molecular dynamic methods, we explore the consequences of mutating some highly conserved residues in the *Ciona intestinalis* Hv1 (CiHv1) permeation pathway. In addition, we explore how the CiHv1 voltage sensor is coupled to permeation by recording gating currents. Mutations at position N264 (located at S4 segment) modified the unitary conductance of the channel. Mutation in a homologue position to N264 in the voltage-dependent phosphatase Ci-VSP, transform this nonconductive voltage sensor into a voltage-gated proton⁺ channel. Our gating currents recordings from the monomeric Hv1 form (Hv1-ΔNΔC) show that voltage sensor activation precedes H⁺ conduction. Channel opening is associated to a second conformational state of the voltage sensor, which accounts for an extremely slow component in the gating current recordings. We hypothesize that in CiHv1 channels the outward S4 movement aligns titratable residues in the different transmembrane segments to form a proton conducting pathway where residue N264 is part of the proton conducting machinery. N264 is also important for the channel selectivity. Our results suggest that the voltage sensor and permeation pathways rely in two different structures allosterically coupled.



SENSORY PHYSIOLOGY AND NEUROMODULATION

REGULATION OF NURR1 IN DEVELOPING DOPAMINERGIC MESENCEPHALIC NEURONS BY MIRNAS

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Nurr1 (NR4A2) is an orphan nuclear receptor that functions as a constitutively active transcription factor. Experiments in Nurr1-deficient mice identified this transcription factor as essential for midbrain dopamine neurons development. In rat brain, at least two Nurr1 mRNA variants are expressed. One has a 3' untranslated regions (3'UTR) of 658 bp long and the other variant is 1339 bp long, which we called Nurr1 short and Nurr1 long, respectively. miRNAs are small RNAs that post-transcriptionally regulate the expression of genes by binding to target motifs in their mRNAs. Predominantly, these binding motifs are found in the 3'UTRs of target mRNAs. The specific deletion of Dicer in postmitotic midbrain dopaminergic neurons produces a progressive loss of these neurons, indicating a key role of miRNA in their survival. In this work, we searched, through a bioinformatic analysis, miRNAs candidates that might regulate Nurr1 translation. Using luciferase gene coupled to the rat short or long Nurr1 3'UTR, we tested the capacity of candidates miRNA to down-regulate luciferase activity. We found that miR-204, miR-302d and miR-93 regulates Nurr1 long variant, exclusively. Using RT-PCR, we found that long Nurr1 mRNA variant is expressed ubiquitously in the mesencephalon during rat brain development and in the adult brain. On the other hand, miR-204 and miR-302d are found exclusively expressed in the dorsal part of mesencephalon in the developing rat brain. Taken together, our data suggest that miR-204 and miR302 restrict Nurr1 expression in dorsal mesencephalon during developing of rat brain.



INTERACTION BETWEEN OREXIN AND OPIOID/NON-OPIOID DYNORPHIN IN PVN IN THE REGULATION OF FOOD INTAKE AND PHYSICAL ACTIVITY

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The orexin/dynorphin (ox/dyn) neurons promote energy expenditure and obesity resistance. Most research has focused on the orexin peptides and how orexin and dynorphin peptides act together to modulate energy balance is not clear. There are opioid and non-opioid DYN peptides, although the opioid DYN have received more attention. Our goal is to evaluate the interaction between orexin and opioid/non-opioid DYN peptides in the control of physical activity and food intake. The hypothalamic paraventricular nucleus (PVN) is important to feeding behavior and physical activity, and our recent work has focused on the interaction between the orexin peptide orexin-A and opioid/non-opioid dynorphin peptides in the PVN. We tested the effects of non-opioid DYN-A₂₋₁₇ and its interaction with orexin-A on food intake and physical activity. To this end, Balb/c mice (n = 4) were cannulated in PVN and, using a repeated measures design, injected with DYN-A₂₋₁₇ (0, 2.5, 5 nmol). DYN-A₂₋₁₇ increased physical activity (P = 0.06) and significantly increased food intake (P = 0.02). Co-injection of DYN-A₂₋₁₇ (1.25 nmol) with orexin-A (150 pmol) into the PVN suggested a potentiation of the response compared with an injection of either peptide alone, however this effect did not reach statistical significance (P = 0.15). To the best of our knowledge, this is the first demonstration of a role of non-opioid DYN actions in energy balance. We are currently expanding upon these results by examining the interaction between orexin and opioid DYN. These experiments will improve our understanding of the mechanisms by which the orexin/dynorphin neurons control energy balance.

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THE NEUROCHEMICAL IDENTITY AND SYNAPTIC TARGETS OF THE NUCLEUS ISTHMI PARVOCELLULARIS OF THE CHICKEN (GALLUS GALLUS)

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In birds, the tectofugal visual pathway is associated to gaze orientation and spatial attention, among other processes. Retinal inputs to the optic tectum (TeO), the main nucleus in this pathway, elicit synchronized feedback signals from two isthmic nuclei, the isthmi parvocellularis (Ipc) and isthmi semilunaris (SLu), both considered cholinergic. The Ipc activity boosts the propagation of retinal inputs from TeO to higher visual areas. This selective modulation would be mediated by acetylcholine release at the superficial tectal layers. However, contradictory findings raise doubts about the cholinergic phenotype of this nucleus. To define the neurochemical phenotype of Ipc along with its synaptic targets in TeO are both essential to determine the mechanisms by which Ipc controls the tectofugal visual output. . We here revise in chicks the neurochemical identity of the Ipc by in situ hybridization assays of mRNAs coding for glutamatergic and cholinergic pre-synaptic markers. We also determined the vesicular glutamate transporter (VGLUT2) protein expression in labeled Ipc axon terminals. To determine the Ipc synaptic targets we double-labeled the Ipc axon terminals and each candidate target structure in TeO by using neural tracers, immuno-histochemical, and electron microscopy techniques. We found that Ipc lacks a detectable mRNA expression of the vesicular acetylcholine transporter (VACHT), but showed a strong expression of VGLUT2 mRNA. Furthermore, anterogradely-labeled Ipc axons showed VGLUT2 immunoreactivity co-distributing with Ipc axon-terminal buttons. We also found that the Ipc axons establish direct synaptic contact, forming a glomerulus-like structure, with the tectal ganglion cells (TGCs), which originate the tectofugal pathway. Our results support a glutamatergic feedback to TeO mediated by the Ipc, concomitant with a cholinergic feedback mediated by the SLu. This work also demonstrates a direct synaptic relationship between Ipc and TGCs, revealing the ultra-structural basis underlying the strong control of Ipc upon the tectofugal visual outflow.



AMPHETAMINE MODULATES NURR1 AND NFkB P65 EXPRESSION IN RAT VENTRAL TEGMENTAL AREA

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Amphetamine is a psychoactive drug with high consumption rates worldwide. The rewarding effects of amphetamine are produced by an increase of dopamine neurotransmission in the ventral midbrain and target nuclei. Nurr1 is a transcription factor essential for the origin and survival of midbrain dopaminergic neurons that also regulates the expression of key dopaminergic genes like tyrosine hydroxylase (TH). Repeated administration of amphetamine causes long-lasting changes in dopaminergic neurons and neuronal damage. In this regard, it has been reported that exposure to psychostimulants modifies NF-kB levels in PC12 cells. NF-kB is a transcription factor that controls inflammatory responses in several cell types. In microglia and astrocytes, NF-kB p65 interacts with Nurr1 to regulate the expression of inflammatory genes. Thus, the hypothesis guiding this work is that Nurr1 and NF-kB mediate gene expression changes after acute and chronic exposure to amphetamine. Adult male Sprague-Dawley rats were injected with amphetamine (1.5 mg/kg) acutely or every day during fourteen days (chronic). Nurr1, NF-kB p65 and TH expression was assessed by western blots in whole extracts of ventral tegmental area (VTA) obtained twenty four hours after the acute or the last amphetamine injection in the chronic treatment. Control rats were injected with equivalent volume of saline. Acute amphetamine administration increased Nurr1, NF-kB p65 and TH protein levels in midbrain nuclei. On the contrary, chronic amphetamine treatment decreased Nurr1 and NF-kB p65, while TH remains unchanged, compared to saline-treated rats. Thus, acute and chronic amphetamine induce opposite effects on Nurr1 and NFkB p65 expression in VTA.



TRANSITORY, FAST CHANGES IN THETA/ALPHA BAND EEG SIGNALS, IN VEGETATIVE STATE PATIENTS DURING RESPONSES TO COMPLEX STIMULI.

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Vegetative state is a conscious disorder characterized by lack of a sustained, reproducible or voluntary behavioral responses to stimulation. Previous reports have showed that subjects in this condition form a heterogeneous group, presenting different evoked and oscillatory response to different complexity stimuli. This remnant activity could be associated with different processing abilities and can be related to the indemnity of some brain regions, or to remaining connectivity between cortico-cortical and cortico-thalamic structures. One way in which these cortico-thalamic connections favor the functional cortical integration is in the generation and temporal modulation of alpha band activity, which is related to a wide range of perceptual and cognitive functions. We propose that transitory changes in alpha/theta band in response to auditory stimuli depend on the different complexity stimuli and reflect remnant connectivity. We recorded data from six subjects in vegetative states and ten control subjects. We measured the evoked and oscillatory activity (24-Channel EEG) to auditory stimuli using a oddball paradigm where the deviant stimulus was the patient's own name pronounced by a family member. We found significant fast changes in alpha/theta band power spectrum in response to deviant stimulus in some vegetative patients. Similar to previously reported in normal subjects, most of the vegetative state patients showed a decrease of alpha power after the deviant stimuli, mostly seen in Cz, around 400-900ms. These results contribute to the model that proposes a lack of cortical integration due to loss of functional connectivity between cortical-subcortical areas, reflecting different degrees of remnant connectivity.



THE OLIVOCOCHLEAR REFLEX STRENGTH AND COCHLEAR SENSITIVITY ARE INDEPENDENTLY MODULATED BY AUDITORY-CORTEX MICROSTIMULATION

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In mammals, efferent projections to the cochlear receptor are constituted by olivocochlear (OC) fibers originated in the superior olivary complex. Medial and lateral OC neurons make synapses with outer hair cells and with auditory-nerve fibers respectively. In addition to the OC system, efferent pathways are also composed by descending projections from the auditory cortex which are directed towards the inferior colliculus, cochlear nucleus and superior olivary complex. The OC function can be assessed by measuring a brainstem reflex mediated by auditory-nerve fibers, cochlear nucleus neurons, and medial OC fibers. Although it is known that the OC reflex is activated by contralateral acoustic stimulation and produces a suppression of cochlear responses, the influence of cortical descending pathways in the OC reflex is largely unknown. Here, we used auditory-cortex electrical microstimulation in chinchillas to study a possible cortical modulation of cochlear and auditory-nerve responses to tones in the absence and presence of contralateral noise. We found that cortical microstimulation produces two different peripheral modulations: (i) changes in cochlear sensitivity evidenced by amplitude modulation of cochlear microphonics and auditory-nerve compound action potentials, and (ii) enhancement or suppression of the OC reflex strength as measured by auditory-nerve responses to 2-4 kHz stimuli, which depended on the inter-subject variability of the OC reflex. Moreover, both corticofugal effects were not correlated, suggesting the presence of two functionally different efferent pathways. These results demonstrate that auditory-cortex electrical microstimulation independently modulates the OC reflex strength and cochlear sensitivity.



CONTRALATERAL EFFERENT EFFECTS ON HUMAN COCHLEAR RESPONSES

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Our brain has the ability to modulate the cochlear response as function of the acoustic stimulation received by the contralateral ear. This modulation is mediated by the activation of the contralateral medial olivocochlear reflex (MOCR). However, many theories of auditory perception and their models, which are used for the development of technologies such as hearing aids or cochlear implants, considered that this responses are fixed. In order to characterize the effect of the MOCR on human cochlear responses, we measured the effect of contralateral white noise (CWN) on absolute tone thresholds, temporal masking curves (TMC) and psychoacoustical tuning curves (PTC) in normal hearing subjects. Perceptual results were analyzed with a phenomenological auditory computer model with efferent control specially designed for this purpose. The main findings were: I) The CWN modifies the response of the perceptual tests, probably due to an activation of the contralateral MOCR. II) greater effects are shown in lower (500Hz) than higher (4000Hz) frequencies. III) The computer model analysis suggests that the CWN reduces cochlear gain and compression and this reduction is greater in the apex region than the basal region of the cochlea.



DEVIANCE DETECTION AND STIMULUS-SPECIFIC ADAPTATION: TO HEAR OR NOT TO HEAR

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The ability to filter frequent and redundant sounds from the rare and unexpected ones is a challenging task for the auditory system. Stimulus-specific adaptation (SSA), i.e., a decreased neuronal response to repetitive stimuli (standard) that does not generalize to rare sounds (deviant), may be implicated in novelty processing observed at larger spatial and temporal scales. We address the properties of SSA by recording extracellular single-neuron responses at different levels of the auditory hierarchy of the anesthetized rat and the awake mice. We use the oddball- and other more complex sequences to determine the presence of SSA and novelty detection. We also used the iontophoresis technique to eject GABAergic and cholinergic agonists and antagonists to manipulate the responses at the synaptic level. We finally used tracer injections and the cooling technique to disentangle the anatomical and functional circuitry underlying SSA. SSA is found in the awake and anesthetized inferior colliculus, medial geniculate body and auditory cortex, but not in the cochlear nucleus. Thus, SSA is first encoded in the inferior colliculus, being stronger in the non-lemniscal pathway, at low intensities and at the neuronal high frequency range. In the inferior colliculus there is SSA for frequency and also for complex sequences. Subcortical SSA is very sensitive to the excitatory-inhibitory balance and is differentially modulated by acetylcholine. Auditory cortex projections exert a gain control effect on subcortical SSA, but SSA is propagated from the inferior colliculus to upper auditory stations.



POSTERS

P1

NEURODYNAMICS OF THERAPEUTIC INTERACTION: PRELIMINARY RESULTS A YEAR AFTER.

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Recently, psychotherapeutic research has focused on the study of patient and therapist mutual regulation. Growing evidence suggests that therapeutic alliance and positive psychotherapy outcomes depends on verbal and nonverbal coordination. Specifically, evidence concerning body movements (e.g. Ramseyer & Tschacher, 2011), facial expression (e.g. Benecke, Peham, & Banninger-Hüber, 2005), rhythm of speech and voice quality (e.g. Tomicic, Martínez & Krause, 2014), and mutual regulation throughout the discourse (e.g. Martínez et al., 2014) has been found. This set of behavioral results, along with others in neurosocial research (e.g. Dumas et al., 2010), suggests that this kind of coordination may have a neurophysiological correlate which participates in the regulatory process in psychotherapy.

The present study intend to provide evidence concerning the dynamic relationship between brain activity and psychotherapy. Here we present the observation device and analytic method of the neurodynamic activity of patient and therapist and preliminary results of a case study performed on an ongoing psychotherapy (30 sessions until now). We show the preliminary results of an analysis of 10 correlative session where simultaneous brain activity of the both participants was recorded during their therapeutic interaction.

BUILDING A MATHEMATICAL MODEL OF THE DIRECTION SELECTIVITY IN A STARBURST AMACRINE CELLS NETWORK.

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Direction-Selective Retinal Ganglion Cells (DSRGC) respond selectively to stimuli moving towards one direction, while a stimulus moving in the opposite direction produces little or no response. This activity is proposed to originate in the Starburst Amacrine Cells (SACs), which release GABA and inhibit DSRGCs when stimulus moves contrary to the preferred direction. Intracellular calcium studies in rabbit's SACs have shown an asymmetrical response to a bar moving through opposite dendrites. SACs highly overlap with each other, and interact through GABAergic inhibitory synapses. However, the role of this SAC-SAC inhibition is not well understood. In silico SAC models have shown an asymmetry in the voltages of opposite dendrites, but until today there is no comprehensive model integrating the bipolar-SAC-DSRGC circuit. We are working in a novel model of the SACs network considering SAC-SAC inhibitory interaction under the PyNEURON simulation environment. Here we show preliminary work in which we optimized the parameters of the GABAergic synapses in a SAC network stimulated by time-dependent bipolar inputs. Our model reproduces stimulus velocity tuning curves and the dependence of the response on the width of the bar stimulus. Future work will be focused in integrating a DSRGC to the model as well as separate ON and OFF bipolar/SAC layers.

MUSIC PERCEPTION IN PRESBYCUSIS

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Presbycusis or age-related hearing loss affects more than 25% of the population older than 65 years old. This clinical entity is produced by a progressive loss of (i) cochlear hair cells, (ii) auditory-nerve fibers and (iii) auditory-cortex neurons. Although it is well established that presbycusis deteriorates oral communication, its effects on music perception are largely unknown. Here we studied musical discrimination in control subjects and presbycusis patients using an automatized and Spanish adapted version of the Montreal battery for the evaluation of amusia (music discrimination impairment). A total of 133 controls (> 18 years old) and 46 presbycusis patients (> 62 years old and hearing thresholds > 35 dB SL) were prospectively recruited. The mean age of control subjects was 48.7 years, while that of presbycusis patients was 76.8 years. The mean accuracy of control patients was 80.97%, while in presbycusis patients was 64.49%. As we found that the educational level and age of the subjects were relevant factors to determine accuracy, we analyzed a data-subset including controls (n=48) and patients (n=46) > 62 years old through Generalized Linear Models. We found that the presence of presbycusis is a relevant factor to explain differences in most tasks, while the educational level is important for all tasks. Furthermore, auditory thresholds were correlated to performance in some tasks while two-syllable speech discrimination scores were not correlated to any task. We demonstrate that independently of age and educational level, music perception is impaired in presbycusis patients.

POLYPHARMACOLOGY OF CNS DRUGS AND BINDING SITE SIMILARITIES: A COMPUTATIONAL STUDY OF DRUGS ACTING SIMULTANEOUSLY AT SEROTONERGIC AND NICOTINIC ACETYLCHOLINE RECEPTORS

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Evidence from systems biology indicates that promiscuous drugs, i.e. those that act simultaneously at various protein targets, are clinically better in terms of efficacy, than those that act in a more selective fashion. This is generating a new trend in drug development called polypharmacology. The basic biological concept underlying these findings is that robust phenotypes such as those observed in mood disorders or neurodegenerative diseases, are the result of a complex network of molecular events rather than changes on a single target functioning. Thus, if only one node of the system is selectively addressed, the network will compensate that pharmacological action, affecting therefore drug efficacy. However, the rational design of promiscuous compounds is a difficult task, particularly when the drugs are aimed to act at receptors with diverse structure, function and endogenous ligand.

In the present work, using docking and molecular dynamics methodologies, we established the most probable binding sites of SB-206553, a drug originally described as a 5-HT_{2B/2C} antagonist and more recently as a positive allosteric modulator at $\alpha 7$ -nAChR. To this end, we build homology models of the 5-HT_{2C} receptor and the $\alpha 7$ -nAChR, respectively. Then, using a statistical algorithm, the similarity between these binding sites was determined. Our analysis showed that the most plausible binding sites for SB-206553 at 5-HT₂ and $\alpha 7$ -nACh receptors are remarkably similar, both in size and the chemical nature of the amino acid residues lining these pockets, giving thus a rationale to explain the affinity showed by the drug upon these two highly different protein targets.

GENE NETWORKS INVOLVED IN AXONAL REGROWTH DURING DIAPAUSE IN *C. ELEGANS*.

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The degeneration of damaged neurons is a key event underlying the pathogenesis of neurodegenerative diseases. To restore the functionality of the neural circuit regeneration of axons is needed. *C. elegans* is a powerful model to test genetics factors affecting axonal regeneration after damage, since its axons can regrow post-axotomy and other paradigms of damage (Ghosh-Roy and Chisholm, 2010). We previously showed that diapause (dauer larva) protects neurons expressing *mec-4d* from degeneration (Calixto et al, 2012) and allows their complete regeneration (Caneo and Calixto, unpublished). MEC-4 is a Na⁺ channel expressed only in the touch neurons, responsible for mechanical response in *C. elegans* (O'Hagan et al, 2005). The dominant mutation *mec-4d* (A713V) triggers the constitutive opening of the channel, Na⁺ entry and increased intracellular Ca²⁺. This in turn activates proteases and triggers an energetic and Redox imbalance leading to necrotic death. Some of the factors that may be influencing neuroprotection and regeneration in dauer are: downregulation of the insulin-receptor DAF-2, activation of DAF-16/FOXO and the increase in antioxidative cellular capacity (Calixto et al, 2012). However, none on these interventions alone produce neuronal regeneration, as in diapause (Calixto, unpublished). To discover the gene networks that determine regeneration in diapause we performed an EMS mutagenesis to find mutants that fail to regenerate their axons. The analysis of each of the mutants was performed inducing diapause by starvation followed by SDS 1% treatment, which kills all but dauers. and morphological analysis by fluorescence microscopy. From the initial 1000 mutants we found 58 candidates that did not regenerate in diapause. We are currently cloning the candidate genes by whole genome sequencing of the mutants. This screen will reveal a network of genes important for regeneration of morphology and function of damaged mechanosensory neurons during diapause. Funding: Anillo ACT1109, Conicyt USA-2013-0041 and Fondecyt 1131038 to AC.

Balance between TRPM8 and Kv1.1-1.2 conductances sets the threshold for cold detection. A modeling study on cold sensitive nerve endings.

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Extracellular single-unit recordings of Cold Sensitive Nerve Terminals (CSNTs) in rodents cornea reveals that steady temperatures are encoded with regular, rhythmic temperature-dependent firing patterns ranging from irregular tonic to regular bursting (static response). Rapid cooling or heating produce a transient increase or decrease in firing frequency, respectively (dynamic response). The ability to detect temperature changes is related to the expression of TRPM8, a temperature-, menthol and voltage-activated cation channel expressed in cold-sensitive neurons (CSNs) from trigeminal and dorsal root ganglia. Small nerve endings cannot be directly patch-clamped and the best source of information on thermotransduction currents are cultured CSNs whole-cell recordings. Using calcium imaging to measure activity in CSNs, it was found that the temperature threshold correlates not only to TRPM8 current density, but also to the I_{K_D} break potassium current, depending on Kv1.1-1.2 channels (Madrid et. al, 2009). In order to test whether these observations may also be valid for CSNTs, where thermotransduction occurs, we are using a mathematic model able to reproduce their dynamic and static responses to cold temperatures. We added a Kv1.1-1.2 channel model to reproduce I_{K_D} and show that the temperature threshold of our models is correlated with TRPM8/Kv1.1-1.2 functional expression ratio, in accordance to the observed in cultured CSNs. Our result supports the hypothesis that this mechanism can be the basis for discrimination between pleasant/noxious cold stimuli. Supported by FONDECYT 1130862(PO) 1131064 (RM) and Anillo ACT-1113 (RM, PO).

THE POSTERIOR LATERAL LINE NERVE AS A MODEL FOR THE STUDY OF NEUTROTROPHIC INTERACTIONS AND NERVE REGENERATION DYNAMICS

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The posterior lateral line (pLL) is a mechanosensory system present in fish and amphibians, composed of discrete sensory organs called neuromasts, where hair cells are located. These cells are excitable mechanosensory cells and are innervated by afferent neurons whose somas are located in the posterior lateral line ganglion. Due to the resemblance of this system with the inner ear of birds and mammals, has been proposed as its evolutionary precursor. The pLL is formed during early development of zebrafish from a migrating primordium that deposits the neuromasts of the trunk and tail. At the same time, the afferent neurons extend their peripheral projections and innervate the neuromasts. The peripheral projections, the lateral line nerve, can rapidly regenerate following transection (neurectomy) and thus it offers several advantages for studying *in vivo* the dynamics of nerve behaviour during regeneration and other phenomena such as neurotrophic interactions.

In our laboratory we have used transgenic lines that express fluorescent proteins in the nerve and other components of the system to study the dynamics of peripheral nerve regeneration and also its dependence on different cells types like Schwann cells and target cells. Our results show that the pLL nerve has a similar behaviour to that described in mammalian peripheral nerves and suggests that this system is a good model for understanding the intrinsic cellular and molecular mechanisms involved in regeneration.

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BASAL FOREBRAIN SOMATOSTATIN-EXPRESSING NEURONS MODULATE NEURONAL ACTIVITY IN THE PREFRONTAL CORTEX OF ANESTHETIZED MICE: AN OPTOGENETIC STUDY

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Impairment of cortical activation has been observed in many psychiatric and neurological disorders. Understanding the underlying neurobiological mechanisms of cortical activation is a prerequisite to treat these dysfunctions. One of the major cortical activating pathways arises in the basal forebrain (BF), a neuroanatomical region that is the primary source of cholinergic inputs to the entire cortical mantle regulating sleep, wakefulness and attention. To establish the contribution of specific neuronal populations in the BF to the generation and maintenance of global bioelectrical activity patterns, we used a transgenic animal model with specific neuronal populations which can be precisely controlled with high spatiotemporal resolution by optogenetic techniques. Experiments were performed in mice expressing both halorhodopsin, a bacterial chloride pump, and Cre recombinase in somatostatin-expressing cells dependent. Thus, we were able to hyperpolarize GABAergic BF somatostatin-expressing neurons in anesthetized mice with pulses of laser light (532 nm, 4 to 68 mW/cm²) delivered to the magnocellular preoptic nucleus. Furthermore, electrical activity in the prefrontal cortex was monitored during BF optical stimulation and analyzed offline in order to identify alterations in patterns of the induced slow wave sleep. Our results show that optogenetic inhibition of BF somatostatin-expressing neurons diminished the low frequency components of the electrocorticogram and this effect was correlated with selective changes in firing patterns of prefrontal neurons. This study suggests that somatostatin-expressing neurons participate in the modulation of different neuronal populations in the prefrontal cortex and control global cortical states.

COREST/LSD1 COMPLEX REGULATES NOTCH PATHWAY DURING CEREBRAL CORTEX NEUROGENESIS

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During cerebral cortex development neural stem cells (NSC) undergo symmetrical divisions that increase their number, or asymmetrical divisions that originate intermediate progenitors (IPC) or generate neurons. Newborn neurons follow an inside out migration pattern to reach their functional place at the cortex. Epigenetic regulation is an important issue to control neuronal differentiation. Previous results performed in our laboratory showed that CoREST knockdown delays normal neurogenesis and increases the number of both, NSCs and IPCs. Those results lead us to hypothesize that CoREST/LSD1 complex regulates Notch pathway. To study the role of CoREST/LSD1 complex we performed in utero electroporation to express shRNAs in NSC. Both, knockdown of CoREST and LSD1 produce an increase of Hes1 positive cells and a decrease Ngn2 positive cells in the VZ/SVZ of developing cortex. To determine whether exist functional interaction between the two pathways, we used conditional knockout mice for Notch1 and electroporated Cre recombinase. We observed a subtle delay in migration when Notch is deleted at E17.5. CoREST knockdown shows a pronounced delay in neuronal migration. If these pathways interact, the loss of both Notch and CoREST should reverse the delay in migration. When we co-electroporated CoREST shRNA and Cre recombinase in floxed Notch1 mice, migration is partially restored. Thus, our results support a role for CoREST/LSD1 complex as Notch pathway regulator during cerebral cortex neurogenesis. More experiments are necessary to characterize which mechanisms are involved.

ROSTRAL INSULA STIMULATION WITH DEEPTMS FOR THE TREATMENT OF OBESITY; REDUCING ANXIETY-RELATED EATING AND CRAVING. AN OPEN LABEL FEASIBILITY STUDY.

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The rostral insular cortex is located deep within the temporal lobe and is involved in various functions, including pain and drug craving. A recent placebo controlled study stimulating bilaterally the prefrontal and insular cortices in smokers with EPOC demonstrated that high frequency stimulation of the insula with Deep Transcranial Magnetic Stimulation (DeepTMS) with behavioral activation can reduce nicotine craving and consumption and lead to abstinence. Here we show the preliminary results of the first open label study using high frequency prefrontal-insular stimulation for the treatment of anxiety and craving in patients with obesity that undergo diet. Preliminary results show that high frequency bilateral stimulation of the prefrontal and insula with behavioral activation ameliorate general anxiety and food craving during diet.

STATE-DEPENDENT CHANGES IN RESPONSE SELECTIVITY GATED BY BEHAVIOR IN FERRET HIGHER ORDER AUDITORY CORTEX

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Neurons in primary auditory cortex (A1) of the ferret enhance their ability to encode task-relevant stimuli through rapid spectrotemporal receptive field (STRF) plasticity during auditory tasks requiring discrimination between classes of reference and target sounds. In general, such task-induced STRF plasticity in A1 leads to enhanced contrast between reference and target stimuli. Recent work reveals that such contrast is further heightened in non-primary auditory areas lying ventral to A1 in fields PSF/PPF in the dorsal Posterior Ectosylvian Gyrus (dPEG). Earlier work suggested that top-down signals from dorsolateral frontal cortex (dlFC) can trigger changes in STRFs in A1. In order to better understand top-down attentional modulation in higher order auditory cortical processing, we investigated responses in ventral-anterior PEG (vaPEG), including areas Pro-PPF, VPr and the adjacent posterior bank of the pseudo-sylvian sulcus cortex (PSSC). Four ferrets were trained on go/no-go conditioned avoidance tone-detection and click-rate discrimination tasks, in which they had to refrain from licking water when presented with a target stimulus. We recorded >180 single-unit responses in awake, head-fixed ferrets during performance of behavioral tasks. Compared to A1 and dPEG, neurons in vaPEG were more broadly tuned, and displayed longer response latencies and durations. Also, vaPEG neurons had weaker phase locking to the envelope of rippled noise stimuli. Often, these neurons displayed more robust responses to ferret vocalizations than to synthetic stimuli. During auditory task performance, we observed several modulatory effects, with a general tendency to selectively enhance responses to target sounds, or enhance the difference between responses to target and reference stimuli, while also suppressing responses to distractor sounds. Our results show striking behavioral effects in vaPEG neurons that suggest that auditory processing in this area lies in the processing hierarchy between sensory encoding in A1, dPEG and abstract sound meaning encoding in dlFC.

ANTI-STRESS EFFECTS AND MEMORY ENHANCER PROPERTIES OF OMEGA-3 FATTY ACIDS IN STRESSED RATS

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Introduction: Chronic stress affects limbic brain areas related to memory and emotions, such as the hippocampus and amygdala. Supplementation with ω -3 fatty acids improves learning and memory of control rats.

Objective: The aim of this study was to evaluate the effects of omega-3 supplementation on the hippocampus and memory of stressed rats, as well as on major biological and behavioral stress markers.

Methods: Male Sprague-Dawley rats were randomly assigned to unstressed and stressed (restraint stress) experimental groups. Afterward, animals were supplemented with ω -3 fatty acids or vehicle. Dendritic morphology and synaptic transmission in the hippocampus were evaluated by Golgi stain and patch-clamp tools. The Y-maze was used to analyze the stress effects on memory. ELISA and the plus-maze test were used to evaluate plasma corticosterone levels and anxiety as stress markers.

Results: Supplementation with ω -3 improved the dendritic architecture of CA3 pyramidal neurons and increased mIPSC in the CA1 of stressed rats. Moreover, ω -3 supplementation improved spatial memory and decreased corticosterone levels and number of entries into the open-arm of stressed rats.

Conclusions: Our results demonstrate that ω -3 supplementation had three beneficial effects on stressed rats: a strong therapeutic effect on hippocampal plasticity, memory improvement, and a strong anti-stress effect.

AMYLOID-B PEPTIDE OLIGOMERS IMPAIRS SPATIAL LEARNING AND THETA RHYTHM

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Alzheimer is a neurodegenerative disease characterized by the accumulation of Amyloid- β peptide oligomers and memory loss, but the mechanisms underlying synaptic dysfunction associated to cognitive disability are not fully elucidated. Here we postulate that the injection of A β Os into rat hippocampus affects theta oscillations and spatial learning and memory. To evaluate hippocampal dependent spatial learning, animals were trained in the Oasis Maze task, under injections of A β Os or saline in the CA3 hippocampal region. Rats were tested during 6 consecutive days of the task, which involved searching for a hidden reward in 1 of 21 equidistant wells on a circular arena. To evaluate theta rhythm impairments, we performed unilateral injections of A β Os into CA3 region and evaluate their impact in the ipsilateral CA1 theta oscillations during navigation. We recorded hippocampal local field potential in A β Os and saline-injected rats while them navigated on a circular maze for 40 minutes per day, for three consecutive days. We found that rats injected with A β Os exhibited an increased number of errors, decreased hit rate and increased walked/expected distance ratio. Furthermore, A β Os decreased theta power oscillation, compared to the control rats injected with saline. These results indicate that A β Os injection impairs theta rhythm power, which possibly underlies spatial learning and memory deficits associated to the disease.

CHARACTERIZATION OF THE SLEEP-WAKE CYCLE IN THE HYBRID MOUSE STRAIN CBA/SV129

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The chronobiology of the sleep-wake cycle (SWC) is determined by circadian and sleep- homeostatic processes. It has been demonstrated that genetic background influences both chronobiological mechanisms, so that mice strains differ in their SWC organization. The hybrid CBA/Sv129 strain has been extensively employed in auditory physiology. Here we explore its sleep-wake cycle to obtain normative data as a part of a research project that relates sleep and auditory physiology. Mice were chronically implanted for EEG and EMG, and were recorded in isolation chambers. After adaptation to recording environment, recordings started under a 12:12=light:dark (LD) cycle and were followed by a recording interval under skeleton photoperiod (SP), for at least three days in each condition. Wakefulness, NREM sleep and REM sleep correspond to 41.1, 48.7 and 10.1% of recording time under LD respectively; and 46.4, 45.7, 7.9% under SP. A significant reduction in total REM sleep, REM/Total Sleep Time ratio, and number of REM sleep episodes is observed under SP respect to LD conditions. Although, a clear 24-hour modulation is evident for sleep-wake states, animals do not display diurnal or nocturnal phase preference for wakefulness or sleep states under both LD and SP. A wakefulness increment is observed around dusk, that mirrors reductions in REM and NREM sleep respectively. CBA/Sv129 strain exhibit an unusual temporal profile of sleep-wake states, with wake predominating at dusk and sleep states distributed during midday and midnight. The studied strain is particularly sensitive to the light:dark schedule. Supported by FONDECYT 1120256 and Fundación Puelma.

GAMMA-BAND ACTIVITY IS NOT NECESSARY FOR CONSCIOUS PERCEPTION BUT IS CONSISTENT WITH PRE-SEMANTIC FEATURE BINDING

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The question of which neural processes give rise to conscious perception (CP) has been of increasing interest. Experimental approaches to tackle this question usually include EEG frequency analysis, which have linked CP with the gamma band (30Hz-80Hz). In detection tasks, an increase in gamma band (particularly $\approx 40\text{Hz}$) appears at two distinct time windows after stimuli presentation. An early component around 200ms, thought to be associated with conscious perception, and a latter one around 600ms that appears to be related with to the subject's response. Recent evidences have also linked early gamma increases to feature binding, a pre-semantic perceptual process not necessarily related to CP. To elucidate whether gamma band increases are necessarily associated with CP we constructed a visual detection paradigm that considerably reduces the amount of perceptual features of the target, but clearly allows for the "seen-not-seen" basic distinction to be made. Thus we aimed to minimize the process of feature binding but to maintain the CP of the target. 11 Subjects were recorded with 32-channel EEG (2048Hz) while performing the task. We compared the spectral power of gamma band in detected versus non-detected trials and assessed the significance of these differences with a permutation method ($p < 0.05$). No statistical differences were found in the first 500ms after the target. The lack of differences in early gamma power using this low-features stimulation paradigm is consistent with the idea that gamma is not necessarily related to CP, and supports early gamma as a correlate of the low-level process feature binding.

ROLE OF HISTAMINERGIC SYSTEM IN THE VENTRAL TEGMENTAL AREA DURING REWARD RELATED TASKS.

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The goal directed behaviors are determined by probabilistic learning and motivational aspect of the process associated to them. The mesolimbic dopaminergic pathway has been deemed as the most relevant neuromodulatory system involved in the operation of these processes, by controlling the motivational state of the subject, and learning the probabilistic relationship between actions and rewards. However the interaction of the dopaminergic system with other components necessary for goal directed behavior of the ascending arousal system, such as the histaminergic system, are still poorly understood. In this work, we studied the effects of bilateral injections of histamine in the Ventral Tegmental Area (VTA) of rats, previous to: i) a progressive ratio task, where the animal (n=5, all male Sprague Dawnley) must press a lever in a geometrically increasing way to get rewards, to measure motivation; and ii) a resistance to extinction task (n=5, all male Sprague Dawnley), consisting on a training session where rewards are given at different probabilities (25,50,75, and 100%), and then no more lever presses are rewarded, to evaluate the resistance to extinction. The animals injected with histamine into VTA, compared to saline vehicle injections, showed a significant decrease in the motivation to get rewards in the progressive ratio and a diminished capacity to extinguish non rewarded behaviors, during the probabilistic rewards paradigm. These results are in agreement with in vitro studies which suggest that the histamine may have an indirect inhibitory effect over the dopaminergic system, helping to unravel the interaction between this neuromodulatory system during goal directed behaviors.

SHIFTING ATTENTION TO A BODILY SIGNAL MODULATES EARLY SENSORY RESPONSES TO CONCURRENT VISUAL STIMULI WHILE INDUCING AN INCREASE IN PARIETO-OCCIPITAL ALPHA BAND ACTIVITY.

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Throughout the day, our attention is either actively oriented (or spontaneously wanders) between many different possible objects. Some of these are external (such as a traffic-light) while others are internal (such as whether we are feeling hungry or whether we remember answering an important email). Here we recorded continuous EEG while subjects shifted attention to their heartbeats and compared it with when they maintained attention to upcoming visual stimuli. We used a paradigm in which, for each trial, a cue stimulus was used to indicate whether the participants had to count either a series of visual target stimuli presented on the screen (visual condition) or their heartbeats (inner condition). Throughout the task a behaviorally irrelevant checkerboard stimulus was presented as attentional probe around the fixation point. ERPs time-locked to the checkerboard stimulus were obtained. Despite maintaining fixation in both conditions, we found that the early P1-N1 amplitude was significantly reduced during the inner condition when compared to both the visual condition and a prior unrelated baseline. In contrast, peak alpha band power over parieto-occipital electrodes was higher while attending inwardly when compared to both the visual task and the baseline. These results are consistent with an amodal, resource-model of visual attention whereby allocating attention to a bodily signal can negatively affect the early sensory response to visual stimuli.

CANNABINOID RECEPTOR TYPE 1 ANTAGONIST (AM251) IMPROVES LEARNING AND MEMORY CONSOLIDATION OF STRESSED RATS

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Introduction: Stress and endocannabinoid (eCB) system modulates brain areas related to learning and memory, such as the hippocampus. eCBs regulates GABAergic transmission by cannabinoid receptor type 1 (CB₁), while chronic stress decreases GABA releases in the hippocampus and impairs memory.

Objective: The aim of this study was to analyze the effects of chronic stress on CB₁ expression in the hippocampus and effects of AM251 on learning and memory of stressed rats.

Methods: Male Sprague-Dawley rats were subjected to chronic restraint stress (21d/6h); control animals were not exposed to any type of experimental stress. Both groups were treated with vehicle (i.p., physiologic serum) or AM251 (i.p., 0.3 mg/kg/day). Afterward, CB₁ expression was evaluated by RT-PCR and learning and memory in the Morris water maze in all experimental groups.

Results: CB₁ expression was upregulated in the hippocampus by chronic stress, while AM251 treatment improved learning and memory consolidation of chronically stressed rats compared to control animals.

Conclusions: These results suggest that AM251 prevented the effects of stress-induced increases of CB₁ expression in the hippocampus, which in turn improved learning and memory of stressed rats. This study opens a new approach to understand the interactions between stress and eCB system in the brain.

MODULATION OF ATTENTION IN A VISUAL DISCRIMINATION TASK INFLUENCE OF MOTOR INTERACTION

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Objective: Perception, attention and action are functionally and anatomically tightly coupled and interactive process. The aim of this study have been investigate the relation between motor preparation and attentional process in healthy and Adhd subjects during carrying out of visual discrimination task requiring sustained visual attention in two experimental conditions (visual & motor condition). Methods: Nine university students (5 control subject and 4 subject with medical history of Adhd in childhood), carried out a discrimination attentional task sat in front a computer with stabilized head by chin rest and made interaction with task using a keypad. In the task, a target ball going across the screen horizontally at a constant rate (5 ° / sec), at a random time between 800-1200 ms. after start the trial, a discrimination target will appear during 60 ms. (two letters resembling either a 'E' or 'F'). The subjects were instructed to tracking closely with gaze the target ball displacements and to report whether discrimination targets had been congruent or incongruent. The target were balanced between congruent (50%) or incongruent (50%), each trial taking 3000 ms. Results: Our results showed there were significant difference ($p < 0.05$) in the percentage of correct discrimination in control subjects between visual and motor condition. By contrast, there were no differences in the subjects with Adhd between the two studied conditions. The mean time spent by subjects to respond Adhd is greater than control subjects (1600 vs. 1200 ms), although this difference is not significant between these groups.

BASAL BIASED PERCEPTION UNDER THE NECKER CUBE BISTABLE STIMULUS.

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On every gaze our brain has to solve the uncertainty of visual physical stimuli, how it is solved will depend on the subjects' expectancies and context. Specifically, previous conscious or unconscious brain states will affect the current brain state, thus biasing or modulating perception. Here, we explore this phenomenon by using a perceptual priming approach. A metacontrast masked-prime was used to try and bias the perception of a bistable stimulus (the Necker cube). The priming stimuli were 1) a white noise image 2) a leftward oriented cube 3) a rightward oriented cube. Overall, when the masked-primer was a noise image, we found a significant bias towards perceiving the leftward cube without significant decrease in response time. This intrinsic bias was not explained by subjects' ocular dominance. When the masked-primer image was the leftward cube, the median latency to respond 'leftward cube' perception is significantly shorter than to report 'rightward cube' perception, without differences in the number of 'leftward cube' reports compared to the noise primer. This tendency to 'leftward cube' perception was attenuated but not reversed when the masked-primer was the 'rightward cube'. We conclude that there is a basal tendency to consciously report one cube perception across subjects, as metacontrast masking occurs at late levels in the visual pathway this results are probably explained by acquired cultural elements, but further experiments in this line are needed.

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STROOP MODIFICADO PARA ESTÍMULOS ALIMENTARIOS: DESARROLLO Y PILOTAJE DE LA TAREA PARA MEDIR SESGO ATENCIONAL HACIA LA COMIDA

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El sesgo atencional ha sido descrito en diversas patologías psiquiátricas, entre ellas Trastornos del Ánimo, Trastornos Ansiosos, Trastornos asociado a Consumo de Sustancias y Trastornos de la Conducta Alimentaria (Anorexia y Bulimia). Existen diversas tareas para evaluar el sesgo atencional hacia la comida, siendo una de ellas el Stroop Modificado para Estímulos Alimentarios o “Food Stroop”. El “Food Stroop” ha sido ampliamente utilizado en estudios con pacientes con trastorno de la conducta alimentaria, siendo una herramienta validada para la exploración de este sesgo. Sin embargo, pocos estudios han incorporado esta herramienta en la evaluación de pacientes con obesidad. Las tareas de Stroop Modificada permiten un registro no invasivo, compatible con la evaluación clínica habitual y se han descrito correlatos electrofisiológicos. En los registros de Electroencefalograma, ha sido consistente el hallazgo de aumento de la amplitud de la P300 y del Slow Potential en pacientes adictos expuestos a estímulos relacionados a drogas. En este grupo de pacientes el sesgo atencional se correlaciona con craving, riesgo de recaída y mal pronóstico. Sin embargo poco se sabe sobre la relevancia del sesgo atencional en pacientes con obesidad. El presente estudio presenta el desarrollo de un Stroop modificado para estímulos alimentarios compatible con nuestra realidad local, así como los resultados obtenidos del pilotaje realizado en sujetos controles, previo a la incorporación de sujetos con obesidad del Centro de Tratamiento de la Obesidad de la Pontificia Universidad Católica de Chile.

GPS-INSPIRED METHOD FOR RODENT TRACKING USING ARDUINO-BASED OPEN FIELD AND FFT ANALYSIS.

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Due to the fact that video-based tracking methods for laboratory rats are expensive and time consuming, a novel approach of the time dependent position was developed. In this work we show a new kind of cage for performing open-field experiments in rodents, based on Arduino microcontroller and pressure sensors. GPS trilateration method was used to obtain the rodent position, where Fast Fourier Transform(FFT), Position over Time and Histogram were used to obtain valuable information for the rat behavior. For the data acquisition, Python language was selected, due to its performance in low latency. On the other hand, Matlab was used for its versatility and quick software prototyping. Video recordings for control rats and schizophrenic-like animal models were acquired, binarized and stored for further analysis, while pressure recordings were also obtained at the same time from the same cage. This allowed us to contrast our method with the video-based tracking method. Pressure recording show the same movement patterns and inherent metadata obtained from video analysis, but the time used to process all the data is faster than the video method. In summary, results suggest that this new technique decreases substantially the amount of time devoted to analysis and may allow online display of results. **Funded by FONDECYT 1130904, Anillo ACT-1113.**

LOCALIZATION OF LANGUAGE REGIONS IN THE HUMAN BRAIN BY FUNCTIONAL MAGNETIC RESONANCE IMAGING USING AN AUDITORY PARADIGM ADAPTED TO THE NATIONAL CONTEXT

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Language, an important human cognitive function, is represented in the left hemisphere in 95% of right-handed and 78% of left-handed people. Broca and Wernicke areas are known to be essential for language processing; however, they exhibit a high variability of specific localization among humans. Their identification prior to any given neurosurgical intervention may help avoid any unwanted side effects on language. The exposure of patients to an auditory paradigm while being evaluated by an fMRI works as a non-invasive method for pre-operative language region identification. This study aims to validate an auditory paradigm with native Chilean accent, capable of determining the dominant localization of language in Chilean population. This because there is evidence that the brain processes accents and dialects differently, that listening to other accents makes language comprehension difficult for listeners and that children recognize accents since the age of one and a half years. So far, two right-handed volunteers have participated. Each was exposed to native and non-native stimuli twice. We found bilateral representation of language with both stimuli, seemingly due to early bilingualism of both participants. By contrasting native to non-native stimuli, we found differences in the medial and left lateral frontal lobe and in the medial occipital lobe. Practically no differences were found after doing the inverse contrast. More subjects are being recruited in order to make more accurate inferences from the results.

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MUSCARINIC ACETYLCHOLINE RECEPTORS ARE REQUIRED FOR OLFACTORY LEARNING AND MEMORY IN DROSOPHILA MELANOGASTER.

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Numerous evidence point out that G protein-coupled, metabotropic receptors are necessary for learning and memory. In *Drosophila melanogaster*, acetylcholine and their receptors are considered the major contributors to neuronal communication in the brain. The metabotropic muscarinic acetylcholine receptor (mAChR) is highly expressed in *Drosophila* Mushroom Bodies (MBs), an insect brain structure associated to olfactory memory. Here we evaluated the functional properties of mAChRs expressed in MBs and their contribution to the generation of olfactory memory.

A well-known pavlovian conditioning paradigm was used to establish an associative learning in flies, by pairing an odor with electric shock. Memory performance was evaluated in flies deficient in mAChRs by using genetic or pharmacological tools: in one hand, the Gal4/UAS system was used to direct an RNAi for mAChR to the MBs; on the other hand, flies were fed with compounds that affect mAChR activity. Calcium imaging technique was used to assess the properties of mAChRs in fly MBs.

Our results show that muscarinic drugs differentially modulate olfactory memory. Moreover, mAChR reduction in MB neurons increases memory acquisition. This learning enhancement is not due to sensorimotor or developmental abnormalities. Cell imaging experiments suggest that the effects of these manipulations on olfactory memories are explained by the activation of mAChRs expressed in MBs.

Altogether, these data show for first time that mAChR negatively modulates olfactory learning and further suggest that muscarinic ligands can modify intracellular calcium levels to contribute to new memories.

NEUROCOGNITIVE EVIDENCE FOR NEUROPSYCHIATRIC MODELS BY MEANS OF INTRACRANIAL RECORDINGS IN HUMANS

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Compared with other cognitive neuroscience techniques (fMRI and ERPs), local field potentials (LFPs) recorded with deep electrodes provide a privileged direct measure of spatiotemporal evoked activity. This approach can be used to test and evaluate current neuroanatomical models of different cognitive processes. Here, we present different examples of how intracranial recording can complement and clarify different neurocognitive models built with other methodologies, namely: motor-language networks and their affectation in motor disease; working memory binding; contextual integration models and social cognition processes. Finally, outstanding questions regarding the possibility of simultaneously stimulating and recording LFPs during resting state and active tasks are discussed.

SPATIAL AND OBJECT RECOGNITION MEMORY AND NON NMDA PLASTICITY IN HIPPOCAMPUS OF OCTODON DEGUS DURING AGING.

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The *Octodon degus* (degu) rodent naturally develops the main signs of Alzheimer disease (AD) during aging, including A β soluble and neurofibrillar tangles, associated with cognitive spatial and object recognition failures, and alterations in synaptic plasticity (reduced LTP and enhanced LTD). We have recently developed several experimental strategies to further understand the etiology of degu neurodegeneration during aging. We report here on the effects of exercise (free access to running wheel vs no access to wheel) in the process of object recognition (OR), and short and long term spatial memory using the 8-Arm maze test. Using these tests, we find that aged degus show impairments after 4 months under sedentary conditions compared with exercised degus of all ages. We are also studying, in behaviorally characterized degus, the presence of an NMDA-independent LTP and LTD mechanism in the hippocampus, in order to understand other possible mechanism involved in degus neurodegeneration. Finally, we have started to characterize the sequence variants of the ApoE4 allele (a genetic risk factor for sporadic AD) present in our colony, , and its possible relationship with AD progression.

SOCIAL EXCLUSION HURTS. AN EXPERIMENT OF TMS ON LANGUAGE AND EMBODIMENT

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Different languages agree in representing social exclusion as a painful experience across different expressions referring to physical pain. In Spanish, the most common expression is “hurting someone’s feelings” to describe the experiences of social exclusion. The metaphorical idea that the pain associated with negative emotions is similar to that experienced pain in a physical injury is increasing, since the evidence suggests that some of the same neural machinery activated in the experience of physical pain, can also be associated with the pain of social rejection. Social exclusion hurts, literally. In this study a group of women received words of social exclusion (eg, rejected) or social inclusion (ie, accepted) superimposed on visual stimuli depicting painful or not painful action applied on the first dorsal interosseous muscle (PDI) of the right, seen from the perspective of the participant. While single TMS pulse applied in the motor cortex and the corresponding motor evoked potential was recorded. The results showed that primings exclusion and social inclusion modulated potential muscle PDI engines differently in the context of painful and non-painful visual stimuli. This interaction indicates that, even in the absence of a social context, the words themselves are a powerful sign of social exclusion that elicits motor resonance circuit empathy for pain. Furthermore, the results support for the first time that language comprehension involves a corporeal exclusion process associated with physical pain.

DOPAMINE D3 RECEPTOR DEFICIENCY INDUCES CHRONIC DEPRESSION, INCREASED ANXIETY AND DECREASE IN TASTE NEOPHOBIA.

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Dopamine has been associated to depression and anxiety-disorders, but the specific contribution of each subtype of dopamine receptors still remains elusive. Here we assess the role of Dopamine D3 receptors (D3R) in depression, anxiety and taste neophobia using D3R knockout mice (D3RKO). D3RKO mice showed depressive-like symptoms as measured by increased immobility time in the forced swim and the tail suspension tests, as well as in anhedonia as measured in the non-motor dependent sucrose test. D3RKO mice also showed increased anxiety-like symptoms measured as an increment in thigmotaxis in the openfield and a significantly lower time spent in the lit compartment in the light/dark exploration test. Finally, D3RKO mice also showed a decrease in taste neophobia to saccharin 0.1%. These results suggest that the dopaminergic system may be involved in depression, anxiety and fear to taste novelty via D3R dependent signaling.

DISTINCTIVENESS IN THE “EEK-EEK” CALLS OF CHINCHILLAS

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Acoustic communication signals can provide relevant cues for individual recognition. Nevertheless, an important requisite is the existence of larger between- than within-emitter signal variation. Acoustic signals are complex traits that can vary in spectral and temporal components, implying that signal distinctiveness can result from differences in single or various acoustic components. Here, we induced domestic chinchillas to vocalize in a distress context. Our main objectives were to describe the acoustic characteristics of the “eek-eek” calls, and to determine which features may be used for individual and/or sexual recognition. Our results demonstrate that the variation of spectral and temporal components of the “eek-eek” calls of chinchillas is larger between than within individuals, suggesting the potential for distinctiveness between individual signalers. Nevertheless, the potential for sex distinctiveness of this call type seems to be limited. Our results combined with previous studies on auditory capabilities of chinchillas suggest that this rodent may become an important model species for studying auditory-vocal interactions under stress conditions.

AN AUTOMATIC PROCEDURE TO STIMULATE AWAKE BIRDS RELATIVE TO GAZE POSITION

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The tectofugal system, the principal visual pathway in most vertebrates, is reciprocally connected to nuclei in the isthmic region forming a highly conserved isthmo-neural network. This network seems to constitute a visual attentional mechanism based on recurrent neuronal activity. Most experiments performed on this system require the use of anesthesia to avoid eye movements, but lately, considering that this is an attentional system, it has been questioned whether anesthesia introduces artifacts. To perform accurate experiments in head-restrained, awake birds, the position of the stimuli must be corrected to compensate for the continuously shifting position of the eye. Here we present a methodology and software implementation to calibrate a pupil tracking software to present stimuli at the adequate location. Our system does not require prior training, complex eye models subject to animal variations nor delicate eye surgery; instead the position of the gaze is estimated based on physiological responses (extracellular potential) to visual stimuli, and thus it is in close relation to the phenomena under study. The calibration requires minimal work by the experimenter as the procedure is highly automated. Moreover, this procedure enables the quick calibration of multiple electrodes. The setup is flexible enough to trigger stimuli under different conditions and could be easily adapted to fit other animal models. We think that this methodology constitutes a strong technological support for a wide range of physiological and cognitive studies in the visual system and a significant improvement on existing techniques.

CORRELATION BETWEEN OLIVOCOCHLEAR REFLEX IN AWAKE OR ANESTHETIZED CHINCHILLAS AND BEHAVIORAL PERFORMANCE IN A TEST USING AUDITORY DISTRACTORS

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Distortion product otoacoustic emissions (DPOAEs) are sounds generated in the cochlea in response to two simultaneous tones. DPOAE amplitude changes produced by contralateral acoustic stimulation (CAS) have been used to measure the olivocochlear reflex (OCR) strength. This reflex can be altered under anesthesia and also shows high intra and inter individual variability. The OC bundle that activates this reflex is located in the brainstem, but cortical descending pathways can modulate its activity. Seven chinchillas (*Chinchilla laniger*) were used to evaluate the influence of OC projections in awake and anesthetized state and four were trained in a visual two-choice task, to investigate the relation between OCR magnitude and behavioral performance. Our results show that CAS-induced reductions in DPOAE amplitudes, are greater in awake than anesthetized chinchillas ($n=7$; Awake: $-3,63\text{dB}$; Anesthetized: $0,02\text{dB}$; $p < 0,001$), which demonstrates that the awake state enhances the effects of CAS. In behavioral experiments, we evaluated selective attention to visual stimulus in presence of auditory distractors. Our preliminary results, show that two conditions could exist: bad performance and weaker OCR (Different Score (DS) Correct Response: $-28,5$ and $0,43\text{dB}$ of shift OC) and good performance and stronger OCR (DS Correct Response: $11,0$ and $1,89\text{dB}$ of shift OC). This tendency suggests that there is a relationship between OC strength and behavioral performance in a selective attention test and that it is not possible to explain the variability of the OCR only by brainstem's projections, but that cortical activity and projections must also be taken into account.

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EFFECT OF THE INTRAHIPPOCAMPAL INJECTION OF A LENTIVIRAL VECTOR EXPRESSING SHRNA ANTI-KLOTHO ON A TEST OF SPATIAL MEMORY PERFORMANCE IN MICE.

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Klotho overexpression has been recently associated with an increased cognitive performance. However, klotho is a protein widely expressed in the organism, and the specific role of klotho in hippocampus has not been elucidated. Here we report the effect of the selective knockdown of hippocampal klotho expression on spatial memory in mice.

Knockdown of the hippocampal klotho gene was generated by the stereotaxic injection of lentiviral vectors expressing shRNA anti-klotho or a scrambled shRNA in the hippocampus of six month old C57b6 females mice. Three weeks after surgery the animals were exposed to the oasis maze task to evaluate spatial memory performance. Subsequently, the animals were evaluated in a random modality of this task as a spatial memory independent control. The trials were video recorded for offline analysis.

The knockdown group had a minor errors average versus scrambled controls and a higher hit ratio during the task. However, knockdown group do not showed an improvement in navigational strategies compared to scrambled controls through consecutive trials. These results suggest that a diminished hippocampal expression of the Klotho gene is associated with an improvement in spatial memory ability in mice, without altering the motor performance during spatial navigation.

PRE-STIMULUS LOCAL NEURAL SYNCHRONIZATION CORRELATE WITH PERCEPTUAL ALTERNATION OF AUDITORY BISTABLE STIMULI

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EEG baseline activity has been shown to influence responses to sensory stimulation. This suggests that perceptual awareness does not solely arise from physical stimulus properties. Here we studied whether the local neural synchrony activity immediately before stimulus presentation indicates how a physically unique but perceptually auditory ambiguous stimulus will be perceived. As an ambiguous auditory stimulus, we used the Verbal transformation effect (VTE) which occurs when a word is repeated over and over again without pause, producing an abrupt change in verbal organization manifested in transitions between meanings within the same word for example the Spanish word "Carro" (Cart in English) is repeated several times, it is also perceived as "Roca" (Rock in English). EEG was recorded from 64 channels. As indicators of local neural synchrony, we measured over a wide frequency range the induced spectral power of local signals. Results show that an increase of Beta (14-18Hz) local synchronization, near 200ms before and 500ms after an auditory perceptual reversal. This supports and extends reports on the influence of brain states prior to stimulation on subsequent perception. We suggest that pre-stimulus beta local synchrony would be associated with a destabilization of dynamic brain organization and activity post-stimulus would be an indicator of perceptual reorganization.

VOLUNTARY VERSUS SPONTANEOUS CONTROL OF BISTABLE STIMULI PERCEPTION

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During bistable perception the brain transform ambiguous stimulation into two mutually exclusive percepts, one of which is consciously perceived while the other is suppressed. This selection can occur spontaneously or by the conscious decision of the viewer. Here we take profit of this fact to try and find the perceptual stabilization periods of both, conscious and spontaneous control of bistable perception. We used Tobii Studio software to present 30 adult subjects with a modified version of the Stroboscopic Apparent Motion (SAM) stimulus for three minutes. When rapidly shinned, this stimuli elicits mutually exclusive perceptions of either vertical or horizontal motion. During continuous viewing, the perception of the movement changes every few seconds. The task involved two conditions: In the 'Spontaneous Condition' subjects were asked to report by a button press whenever perception spontaneously changed from vertical to horizontal movement or vice versa. In 'Voluntary Condition' subjects were asked to voluntarily hold horizontal perception as long as they could, and report by a button press when perceptual changes occur. The analysis of the perceptual stabilization period will allow us to determine if the spontaneous control differs from voluntary control. Additionally, we will determine the frequency distribution of both experimental conditions, and compare it with a gamma distribution.

ROLE OF ASTROCYTES IN STRESS, ANXIETY AND DEPRESSION

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Astrocytes are interconnected to allow collective metabolic and electric coupling, sharing their cytoplasmic content via Gap junction channels formed by two hemichannels. Hemichannels that do not form gap junction channels may allow intracellular-extracellular communication. Recent evidence indicates that astrocytes can modulate synaptic plasticity by releasing neuroactive substances known as gliotransmitters which are necessary for fear memory consolidation in the basolateral amygdala. Here we hypothesized that hippocampal connexin hemichannels may be involved in the pathogenesis of depression and anxiety. We have studied the role of astrocytes in anxiety and depression using chronic cannulae implants and in vivo pharmacology, ex vivo measurements of hemichannel activity and drug design. We found that astrocytic connexin hemichannel activity is increased during acute stress and increased even further during chronic stress and that intrahippocampal injection of peptides capable of opening astrocytic hemichannels can induce anxiolytic and antidepressant effects. In consequence, we propose that gliotransmitter release from astrocytes through hemichannels may play a role in stress responses and in the pathogenesis of anxiety and depression.

COMPARATIVE DEVELOPMENT OF THE CHOLINERGIC EPITHALAMIC PATHWAY IN MAMMALS AND ITS POSSIBLE ROLE IN LOCOMOTOR BEHAVIOURS.

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In the vertebrate brain, the cholinergic system has been linked to behavioural mechanisms such as sleep-wake patterns, learning, memory and spatial navigation. The projection from the medial habenula (MHb) to the interpeduncular nucleus (IPN) is the main cholinergic circuit connecting the limbic forebrain to the tegmentum. In turn the IPN forms part of a local tegmental network that in addition to influencing prefrontal and hippocampal cortical activities also modulates brain regions that control locomotor behaviours. However the role of these circuits in the establishment of early motor skill is currently unknown. To start addressing this issue, we propose a comparative developmental approach based on two rodent species with distinct timing of locomotor development, the altricial *Rattus norvegicus* and the precocial *Octodon degus*. We have compared the morphology and developmental timing of MHb-IPN cholinergic projections among these species using Nissl staining and choline acetyltransferase (ChAT) immunoreactivity. We found that axons from the MHb reach the IPN earlier in *O. degus* than in *R. norvegicus*. These results suggest that the timing of development of habenula-IPN system correlated with the timing of the onset of locomotor patterns in these distinct species. Thus, our work could constitute an interesting approach to the study of the role of the habenula-IPN system in the emergence of early motor patterns.

ANTIDEPRESSANT EFFECTS OF OMEGA-3 FATTY ACID SUPPLEMENTATION IN A RAT MODEL OF DEPRESSIVE-LIKE BEHAVIORS

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Introduction: Omega-3 fatty acid supplementation improves antidepressant treatment in human, while in animal models have a strong anti-stress and anxiolytic effects.

Objective: The aim of this study was to evaluate the effects of omega-3 supplementation on the development of depressive-like behaviors.

Methods: Male Sprague-Dawley rats were subjected to chronic unpredictable stress (CUS), an animal model of depressive-like behaviors. Afterward, animals were supplemented with omega-3 fatty acids (DHA and EPA mix) or vehicle. Anhedonia (loss of pleasure) and hopelessness are the core symptoms of major depression, both were evaluated in the rats as depressive-like behaviors by saccharin consumption and forced swim tests (FST), respectively.

Results: Rats that were exposed to CUS showed reduced saccharin intake and floating behavior in the FST, while supplementation with omega-3 prevented these alterations.

Conclusions: Our results suggest that omega-3 supplementation had antidepressant-like effects in rats exposed to CUS. We speculate that omega-3 supplementation could be used in the treatment of stress-related disorders such as depressive and anxiety disorders.

A CLOSE LOOK AT THE ANATOMY OF AN ATTENTIONAL NETWORK IN THE MESENCEPHALON OF THE CHICK (GALLUS GALLUS)

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In birds, the tectofugal visual pathway receives nearly 90% of the retinal projections and is associated with spatial attention and motion perception, among other processes. Retinal inputs to the optic tectum (TeO) establish synaptic contacts with tectal ganglion cells, which are the origin of the tectofugal ascending projection. The tectofugal visual output is strongly modulated by feedback signals from the isthmic complex which comprises the nuclei: *isthmi pars parvocellularis* (Ipc), *isthmi pars semilunaris* (SLu) and *isthmi pars magnocellularis* (Imc). Ipc and SLu are homotopically connected to the TeO, whereas the Imc feedback projection is heterotopic. The tectal 'Shepherd's Crook' (ShC) neurons of the layer 10 are the sole visual input to the isthmic nuclei. They possess a conspicuous bipolar morphology, which presumably integrates retinal inputs along with top-down inputs from higher visual areas, conveying them both to the isthmi. Despite their relevance, it is unknown whether there are different types of ShC which respectively project to separate isthmic nuclei, or a single type which sends axonal collaterals to more than one nucleus. Electrophysiological recordings of single isthmic cells indicate different inputs, but the close synchrony between the visual responses recorded in separate nuclei suggests the opposite. The present work investigated the tecto-isthmic projection by performing *in vitro* injections of neural tracers and "cell-filling" experiments. Double injections of fluorescent tracers in the Ipc and Imc revealed a substantial proportion of double labeled ShC along with single-labelled neurons. Furthermore, cell-filling experiments showed some ShC spreading axon collaterals to both the Ipc and Imc. These results indicate that a significant proportion of ShC cells project to more than one isthmic nuclei, presumably providing a common input that synchronize neural responses across nuclei.

STUDY OF THE NEURONAL ACTIVITY OF THE INTEROCEPTIVE INSULAR CORTEX IN THE INNATE FEAR.

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The insular Cortex (IC) receives sensory information from a variety of interoceptive receptors distributed in nearly every structure of the body that send projections to the interoceptive pathway. This structure integrates information about the bodily needs and makes this information available to higher-order cognitive and emotional processes. Studies in humans that are heavily based on animal models indicate that the continuous processing of bodily signals in the Interoceptive Insular cortex (pIC) is critical for perception of bodily states. However, the precise role of the pIC in innate fear responses and how fear-related body information is represented in the pIC remains unknown. We tested the idea that the emotional responses evoked by stimuli that cause innate fear are represented in the pIC. We investigated whether the pIC is necessary for expression of innate fear. Using a long term sodium channel blocker, Neosaxitoxin, we found that the inactivation of the pIC reduced the freezing to predator odor stimulus. In contrast, the inactivation of the pIC had no effect on risk assessment behavior. Additionally, we recorded the neuronal activity of the pIC during exposure to predator odor. We found correlations between the neuronal activity of the pIC and the expression of freezing and risk assessment behaviors, suggesting an involvement of the pIC in the perception and expression of innate fear.

GLUCOCORTICOIDS IN THE INSULAR CORTEX: ANXIOLYTIC EFFECTS?

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Glucocorticoids (GCs) released during stress and arousal mediate stress responses in the brain. Although GCs are known to participate in arousal-induced memory enhancements, little is known about their role on the behavioral responses to stress and arousal. In this work, we evaluate the possible role of GCs in the response to arousal induced experiences by testing the effects of intra-insular and systemic infusions of GCs in arousal induced neophobia. We used adult male rats implanted chronically into the insular cortex and injected intracranially or subcutaneously 10 min taste presentation of a novel 0.1% saccharin solution as a choice to water, in a low arousal (LA; homecage) or high arousal (HA; novel cage) context. Experiments included: 1) intra-insular corticosterone dose curve; 2) subcutaneous metyrapone and intra-insular corticosterone and 3) subcutaneous epinephrine and intra-insular corticosterone. GCs decreased neophobia in LA and HA. Blockade of GC synthesis (metyrapone) decreased arousal-induced neophobia, effect that was blocked by intra-insular corticosterone. Finally, intra-insular corticosterone blocked epinephrine-induced increase in neophobia in LA. We propose that GCs in the insula may have anxiolytic effects in arousal induced neophobia depending on concurrent level of adrenergic activation.

PRENATAL STRESS DOWNREGULATES REELIN EXPRESSION BY METHYLATION OF ITS PROMOTER AND INDUCES ADULT BEHAVIORAL IMPAIRMENTS IN RATS

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Prenatal stress causes predisposition to cognitive and emotional disturbances. The extracellular protein Reelin, plays critical roles on cortical lamination and synaptic maturation, and its deregulation has been associated to maladaptive conditions. In the present study, we address the effect of prenatal restraint stress (PNS) upon Reelin expression and signaling in pregnant rats during the last 10 days of pregnancy. Animals from one group, including control and PNS exposed fetuses, were sacrificed and analyzed using immunohistochemical, biochemical and molecular biology approaches. We scored changes in the expression of Reelin, its signaling pathway and its promoter methylation. A second group included control and PNS exposed animals maintained until adulthood for behavioral studies. Using the optical dissector, we show decreased numbers of Reelin-positive neurons in cortical layer I of PNS exposed animals. In addition, neurons from PNS exposed animals display decreased Reelin expression that is paralleled by changes in components of the Reelin-signaling cascade, both in vivo and in vitro. Furthermore, PNS induced changes in the DNA methylation levels of the Reelin promoter in culture and in histological samples. PNS adult rats display excessive spontaneous locomotor activity, high anxiety levels and problems of learning and memory consolidation. No significant visuo-spatial memory impairment was detected on the Morris water maze. These results highlight the effects of prenatal stress on the Reelin expressing neuronal population, and the endurance of behavioral consequences in the adult. We also propose an in vitro model that can yield new insights on the molecular mechanisms behind the effects of prenatal stress.

THE ROLE OF THE ADRENERGIC SYSTEM IN AROUSAL INDUCED TASTE NEOPHOBIA IN RATS.

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Stress is a major cause of disease and disability. Stressful events induce the release of epinephrine into the bloodstream from the adrenal gland which in turn triggers the release of brain norepinephrine. Understanding how adrenergic activity in cortex influences behavior during arousal induced experiences may lead to the discovery of new therapeutic targets. Therefore, in the present study we investigated whether adrenergic activity modulates arousal induced neophobia at the insular cortex (IC) in rats. Bilateral microinjection of different doses (1, 10, 100 ug/0.5 ul) of norepinephrine and (1, 5, 10 ug/0.5 ul) of non-selective beta blocker propranolol into IC were tested for arousal induced taste neophobia (using saccharin 0.1% as a choice to water). Systemic epinephrine and intra-insular norepinephrine both increased neophobia in a low arousal context (LA; rat's home cage) while systemic and intra-insular propranolol reduced neophobia in a high arousal context (HA; novel cage). Furthermore, intra-insular propranolol was able to block the increase in neophobia induced by systemic epinephrine in LA. Our findings indicate that adrenergic activity modulates arousal-induced taste neophobia acting directly in the insular cortex. More studies are needed to elucidate the contributions and possible synergic effects of stress hormones in arousal induced behaviors.

CONVERGENT MULTIMODAL INFORMATION IS INTEGRATED AND CODIFIED AS SINGLE EVENTS IN THE HIPPOCAMPUS IN BEHAVING RATS.

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An increasing number of evidence demonstrate the important role of the hippocampus in declarative memory, especially its importance in spatial mapping in which pyramidal cells fire during navigation in specific regions of the space. However, in spite of loss-of-function studies have revealed the key role of the hippocampus in non-spatial tasks, such as object-context association or working memory tasks, is still unclear how non-spatial sensory information related to events it is codified in the hippocampus. Through electrophysiological recordings we will study the electric activity dynamics in dorsal hippocampal pyramidal cells in behaving rats during a multisensory Go/No-Go task, in which the rats must to discriminate between an event that signals a reward ($\text{Go}_{\text{audiovisual}}$) and another that indicate a punishment ($\text{No-Go}_{\text{auditory}}$). Our preliminary results show that animals actually discriminate between two distinct events, even when Go stimuli have been split into unimodal cues ($\text{Go}_{\text{auditory}}$ and $\text{Go}_{\text{visual}}$), suggesting that a single event can be discriminated from another by different sensory cues, generating a proper strategy in consequence such as go for a reward as well as to avoid a punishment. Now we are expecting for electrophysiological data to complement these behavioral observations, to elucidate whether different modalities related to a single event can converge in the hippocampus triggering a similar neural code, and whether combination of different modalities integrates at liminal intensities increasing the relevance of the percept, a phenomenon called multisensory integration.

PREFERENCE TO FACES IN THE GAZE TARGET SELECTION

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Humans move our eyes several times per second to gain detailed visual information. There is an open question how we select the next gaze targets. Do we recognize them before saccades, or after foveating? To address this question, we asked participants to report identity of object images (recognition task) or to view images freely (free-viewing task). An array of four object images were selected from a set of 59 images (human faces, animals, insects, fruits, vegetables, vehicles, and items) and were presented 0.1 s in the recognition task or for 3 s in the free-viewing task at 13 degree of visual angles from the fixation spot. During the recognition task, participants recognized human faces presented at the peripheral position, but failed to recognize other objects at the same eccentricity. In free-viewing task, faces attracted first fixations regardless of its saliency values. On the other hand, if faces were not included in the stimulus array, objects with the highest saliency values attracted first fixations. These results are consistent with an idea that faces in periphery are recognized before saccades and selected as gaze targets, while non-face objects are not recognized in periphery and selected as gaze targets according to the saliency.

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A NEW ACTOR IN THE NEURAL CONTROL OF GAZE: THE VENTRAL NUCLEUS OF LATERAL GENICULATE (GLV)

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The ventral nucleus of the lateral geniculate (GLv) is a prominent retino recipient structure highly conserved in vertebrates. In spite of this, its role in visual operations remain at present unknown. In the present work we establish for the first time in vertebrates that GLv is key actor in the generation of visually orienting gaze shifts.

Specific locus within the pigeon GLv were microstimulated with electrodes chronically implanted. Eyes movements were measured in head restrained animals with a video based eye tracker system. Head movements, in the 3 spatial axis, were measured in unrestrained birds by means of a set of accelerometers and gyroscopes attached to the head.

We found that electric microstimulations of a specific GLv locus triggered the bird to lead its beak to a specific spacial point in a locus-dependent manner. Elicited movements were independent of intensity, frequency and duration of the stimulus. The end position of the beak tip was correlated with the spatial location of the visual field of the stimulated locus. These movements differ in kinematic properties to the ones obtained in the same animals prior to the tectal ablation.

Microstimulations in the pigeon ventral nucleus of lateral geniculate were enough to trigger head and eyes orienting movements, notwithstanding ablation of optic tecta.

BILATERAL CONNECTIONS OF A SATELLITE NUCLEUS IN THE MIDBRAIN TEGMENTUM MAY MEDIATE BINOCULAR INTERACTIONS IN THE RODENT SUPERIOR COLLICULUS.

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The parabigeminal nucleus (PBN), described as a satellite nucleus of the superficial (visual) superior colliculus (SC), is considered homologous to part of the isthmus complex (IC) of non-mammalian vertebrates. In several vertebrates, particularly in birds, the IC is thought to play a central role in attention and stimulus selection. In amphibians, the IC also provides a bilateral projection to the SC, which mediate binocular responses. Cytoarchitecturally, the PBN is a compact cell group lying along the lateral midbrain tegmentum, below the brachium of the inferior colliculus. The precise distribution of cells projecting from SC to PBN and that of PBN terminals in SC is currently unknown. We studied the organization of the PBN-SC circuitry in a diurnal rodent with a well-developed visual system, the *Octodon degus*, by using two neural tracers: PHA-L and CTb. CTb injections in the SC resulted in retrograde bilateral labeling in the PBN and anterograde labeling of fibers only ipsilateral to the injection site. A mixture of PHA-L/CTb injected in the PBN produced labeled cells ipsilateral in the SC, and terminals labeling bilaterally in the SC. The labeled tectal cells are distributed in the superficial layers, across the SC, featuring radial bipolar dendrites, characteristic of the “narrow field” cell types of the superficial SC. The PBN ipsilateral fibers terminate principally in the lateral aspect of the SC, while contralateral terminals show a clear bias towards the medial SC. Our results show a complementary pattern of the parabigeminal projections upon both colliculi. Interestingly, in the medial aspect of the SC, which received contralateral PBN afferents, a portion of the dorsal visual field is mapped. This region has a binocularity of approximately 45° in the *degus*, suggesting that in rodents, like in amphibians, the PBN would be involved in binocular operations at the SC level.

PATTERNS OF GLUTAMATE RESPONSE IN OFF BIPOLAR CELLS OF RAT RETINA

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To date, four morphologically different OFF bipolar cell types have been described in rat retina (#1 to 4). Electrophysiological characterization of these cells is incomplete and is not correlated with morphology for each type. In mouse, a fifth OFF bipolar cell classified as 3b has been characterized by immunohistochemistry. This cell type is PKARII α -positive and HCN4-immunonegative, but morphologically identical to type 3a. However, the glutamate response in 3b has not been characterized and it is unknown whether a homologue cell type exists in other mammalian species. In this work, we used whole-cell patch clamp in acute retinal slices to classify different types of rat OFF bipolar cells by their specific voltage-dependent currents and glutamate responses. GYKI-52466 and SYM2081 were used to isolate responses mediated by AMPA and kainate receptors. The response patterns were correlated with cell morphology by fluorescent tracer injection followed by immunohistochemistry to label HCN4 and PKARII α in type 3 bipolar cells. Our results indicate that rat retina contains two different populations of type 3 bipolar cells, one of which is PKARII α -positive, supporting homology with mouse type 3b. Interestingly, some OFF bipolar cells, especially type 4, present a glutamate response pattern with a fast component, and a slow one, which depend on differential activation of kainate and AMPA receptors, respectively. In conclusion, rat retina contains five different functional types of OFF bipolar cells, whose glutamate response patterns confer a temporal identity to each retinal OFF response channel.

GAP JUNCTIONS INVOLVED IN SPIKING ACTIVITY FROM GANGLION CELLS

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The mammalian retina is a well-organized multilayer neural structure sensitive to light. The retinal ganglion cells (GC) fire spikes in response to visual patterns, creating a neural code that is sent to the brain. Recently, ganglion cells population response has been assessed using multi-electrodes arrays obtaining the simultaneous recording from hundred neurons. Electrical synapses present in most of neurons of the mammalian retina are reported to contribute to several visual functions - including movement sensitivity - of the retina neural network. Here we studied in a diurnal rodent the GCs population activity for control and pharmacological treated retinas, using 18- β -glycyrrhetic acid (b-GA), a general connexin blocker. Using series of dark and light UV or Green LED flashes we have shown an important GC diversity on the light response pattern as well to a flash omission. Under 25-50 μ M of b-GA treatment, retinal pathway connected through gap junctions were disrupted, we observed that some of the GC pattern response are clearly altered. Other parameters as the size of receptive field, time to peak response, mERG response, spontaneous activity were studied both in control and b-GA conditions. The results suggest that some of the retina light pathway used for omission flash response is under the modulation of electrical gap junctions.

CHEMOSENSORY CILIA OF OLFACTORY SENSORY NEURONS INCORPORATE GLUCOSE FROM SURROUNDING MUCUS IN THE OLFACTORY EPITHELIUM TO SATISFY ENERGY DEMANDS OF ODOR TRANSDUCTION.

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Olfactory cilia are long and thin (60x0.2 μ m) organelles devoid of inner membranes, protruding from the apical olfactory sensory neurons (SCNs) dendritic knob. Odorant-activated G-protein coupled receptors lead to opening of Ca^{2+} -conducting cyclic nucleotide-gated channels (CNGs), mediated by a cAMP-cascade. Ca^{2+} activates Cl^- channels, generating a depolarizing receptor potential. The cilia demand high ATP levels during chemotransduction, needed by adenylyl cyclase, ATPases and kinases. The nearest mitochondria (3-4) are in the knob. Slow ciliary ATP diffusion and limited ATP basal levels suggest that the cilia require an additional ATP source to sustain transduction under intense stimulation. Nuñez-Parra et al (PlosOne, 2012) found glucose transporters in supporting cells (SCs) somata and olfactory epithelium ciliary layer, populated by OSNs cilia and SCs microvilli, suggesting a directional glucose transit through the epithelium towards the mucus. We hypothesized that SCs release glucose to the mucus from where it is internalized by the cilia to generate ATP by glycolysis. Immunocytochemistry confirmed the presence of GLU-3 glucose transporter in OSN cilia and SC microvilli. The cilia incorporated a fluorescent glucose analog added extracellularly. Immunoblotting of ciliary membranes revealed glycolytic enzymes. Field epithelial and single SCN recordings showed that glycolysis or oxidative phosphorylation inhibition impaired odor responses. These results suggest that olfactory cilia use two complementary ATP sources, oxidative phosphorylation in the knob and glycolysis in the cilia

EVENT RELATED POTENTIALS (ERPS) DURING FREE VIEWING OF IMAGES WITH INCREASING SEMANTIC COMPLEXITY IN SUBJECTS AFFECTED WITH SCHIZOPHRENIA.

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Schizophrenia (SCZ) is by a global progressive deterioration of cognitive processes. Electroencephalic (EEG) differences between SCZ patients and controls have been reported for many of these cognitive impairments using complex and specialized task that not necessarily resemble natural stimuli/environment to which the brain is adapted. We tested if SCZ global cognitive deficits could be described by EEG features using a more ecological and simple approach. For this purpose, we compared ERPs obtained during free exploration of images with three different levels of semantic complexity in 11 patients schizophrenia and 9 aged-matched healthy controls (HC). Images categories included Plain Gray (G), Pink Noise (PN) and Landscapes (L). EEG was recorded during image visualization. ERPs locked to image onset were obtained from occipital electrodes. We found that there were no differences in ERPs between SCZ and HC in no-semantic content images (G and PN). However, during exploration of landscapes, we found that SCZ exhibited reduced amplitude of the 500 ms component (1.44 ± 0.46 iV) compared to HC (4.15 ± 0.46 iV). This study shows that EEG features could differentiate between SCZ and HC in a simple, instruction-free visual task; thus, this paradigm could be used as a biomarker of SCZ, eventually helping diagnosis and treatment. Supported by: BNI ICM P09-015-F, CENEM ICM P10-001-F and Fondecyt-Postdoctorado 3140306 to CD.

MOLECULAR AND FUNCTIONAL CHARACTERIZATION OF THE Ca^{2+} -ACTIVATED CHLORIDE CHANNEL CLCA4L FROM THE CHEMOSENSORY CILIA OF OLFACTORY SENSORY NEURONS

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Odor binding to G-protein coupled receptors in olfactory cilia triggers a cAMP cascade, where cAMP gates the non-selective cation channel CNG. CNG opening increases intraciliary Ca^{2+} , which gates Ca^{2+} -activated Cl^- channels (CaCC) that amplify the depolarizing current. This channel is thought to be the Anoctamine channel Ano2. With PCR and immunochemistry we found the ClCa4l channel in olfactory cilia, belonging to the ClCa family of CaCCs (Gonzalez-Silva et al. 2013). We further characterized the channel by cloning, sequencing and heterologous expression. Total olfactory epithelium mRNA extracted by Trizol was treated with RNase-free DNase. mRNA was transcribed with the reverse transcriptase Superscript III and oligodT to generate the first cDNA strand. For cDNA amplification by PCR we used several sets of specific ClCa4l primers. Full length cDNA was obtained after several PCR rounds. The products inserted in pUC18 were amplified and sequenced. Homology search was performed on the BLAST server. The coding sequence showed 99% homology with ClCa4l. HEK293 cells were transfected with EGFP-encoded vector pIRES-EGFP-ClCa4l plasmid. Transfected HEK293 were used 3-9 days post-transfection for expressed ClCa4l patch-clamp characterization. The transfected ClCa4l cDNA conferred to the cells a Ca^{2+} -activated Cl^- -selective current, sensitive to the Cl^- channel blocker niflumic acid. The results strongly support the presence CaCl4l in olfactory cilia

ON THE ORIGIN OF THE TYMPANIC ELECTRIC NOISE IN HUMANS.

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In animal studies, the power spectrum of the spontaneous activity recorded with a cochlear electrode located in the round window shows an energy peak centered around 800 to 1000 Hz. The proposed origin of this component is the spontaneous activity of auditory-nerve fibers, as each action-potential, lasting 1-2 ms, contributes to the signal in that frequency band. Here, we used a non-invasive method to record -for the first time in humans- this neural noise by means of a tympanic wick electrode. We recorded a total of 25 volunteers, referenced to vertex or to the contralatareal earlobe. Recordings were performed under silent or in response to stimuli of different modalities, including auditory, vestibular, somatosensory and motor activity. Although all subjects showed a peak of spontaneous activity at 1000 Hz, there was a considerable variability between individuals, which depended on electrode impedance. The most reliable responses were obtained with vestibular stimulation by either high (air flow at 49°C) or low (24°C) temperature caloric tests, which produced an increase in the magnitude of the energy at 1000 Hz. On the other hand, only in one subject (out of 12) we obtained an auditory response to a broad-band noise which displayed a peak around 800 Hz. These results demonstrate that electric noise from the tympanic membrane is originated from a biological source, suggesting that the 1000 Hz component has a mixed origin, probably including brainstem networks, like the vestibular pathways. However, it still remains unknown whether the 800 Hz peak response reflects the auditory-nerve activity.

ONTOGENIC DEVELOPMENT OF THE ACCESSORY OLFACTORY SYSTEM IN OCTODON DEGUS.

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The Vomeronasal System (VNS) is involved in the modulation of social and reproductive behaviors in mammals. The sensory epithelium of this system is located at the Vomeronasal Organ (VNO), and contains neurons expressing different kinds of semiochemicals receptors. Projections of these neurons target the Accessory Olfactory Bulb (AOB), where they segregated into two subdomains, rostral (rAOB) and caudal (cAOB). Some Caviomorphs rodents exhibit large size differences between both subdomains. In adults *Octodon degus*, the rAOB doubles the volume of the cAOB, and also features more and larger glomeruli, along with a greater number of Mitral/Tufted projections neurons. However, it is not known when these differences are established in ontogeny. We performed an anatomical study of the ontogeny of the AOB in *Octodon degus*, characterizing this structure along a series of several prenatal and postnatal stages ($n > 5$ in all cases), by means of various histological and immunohistochemical methods. We found that AOB subdomains can be distinguished during prenatal stages, but lacking of anatomical mature-like traits, which become established at early postnatal stages (0-15 dpn). During this same period, the volume of the mitral/tufted cell layer (MTL) acquire a bias toward the rAOB, being this 25% greater than cAOB at 15 dpn ($Z = 2,20; p = 0,03$; mean value $\pm$ SE). No significant bias in the volume of the Glomerular Layer (GL) can be appreciated in this same period ($Z = 1,61; p = 0,1$). GL volume bias towards the rAOB developed during later postnatal stages, being 11% greater at 30 dpn ($Z = 2,19; p = 0,03$), and 20% greater at 60 dpn. These results suggest that the maturity of the VNS glomerular neuropile, and hence the establishment of the differences between its subdomains, may be influenced by early semiochemical experience.

RETINAL PROJECTIONS AND VISUAL FIELDS OF THE BAND-WINGED NIGHTJAR (*CAPRIMULGUS LONGIROSTRIS*), A NOCTURNAL INSECTIVORE BIRD.

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Nocturnal birds have many sensory specializations, such as frontally oriented eyes and increased prevalence of certain visual projections, which are related to living in scotopic environments. Those features have been thoroughly studied only in nocturnal birds of prey. Nightjars (Caprimulgiformes) are predators that capture flying insects at night. Their visual system has been partially described, but its detailed neuroanatomy remains unknown. In this study we describe the visual fields and retinofugal projections of the Band-Winged Nightjar (*Caprimulgus longirostris*). The extent of the visual fields of nightjars was determined using an ophthalmoscope reflex technique. The visual field extends frontally, with a posterior blind area of 80°, and a binocular convergence covering the dorsal-anterior field, with a maximum extension of 40°. An anterograde neuronal tracer (CTB) injected into the retina was used to reveal the retinofugal projections. Labeling was found only in the contralateral retinorecipient nuclei. At the thalamofugal pathway, nucleus opticus principalis thalami receive a massive retinal innervation, segregated in specialized subnuclei. At the optic tectum, retinal fibers span densely from layers 2 to 8, with some very unusual fibers ending in layer 9. A dorsal thickening was found in layers 2 and 4, but not in layer 5. Our results suggest that nightjars have a tectal specialization covering roughly the extent of their binocular visual field. The unusual anatomy of the retinotectal terminals, reaching deeper layers than in any other adult bird, may be related to nightjars' nocturnal insectivorous behavior. Nonetheless, a clear interpretation of those features requires further studies.

MISPLACED PRETECTAL, AND NOT THALAMIC, CELLS ORIGINATE THE ODD MAMMALIAN “THALAMO-TECTAL” DESCENDING PROJECTIONS. A STUDY IN THE CHILEAN RODENT OCTODON DEGUS.

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In all classes of amniotes a prominent feature of the so-called tecto-fugal visual pathway is a massive bilateral and diffuse projection from the Optic Tectum/superior colliculus (TeO/SC) to the thalamus. In rodents this tecto-recipient thalamic territory corresponds to the caudal division of the pulvinar complex (Pulc). A previous work in the squirrel has also reported the presence of retrogradely labeled cells in the Pulc after injections of the neural tracer CTb in the SC. This projection appears to be an oddity, given that the whole dorsal thalamus is considered to generate only ascending projections towards different telencephalic areas. We replicated those experiments in a diurnal chilean rodent, the *Octodon degus*; after tectal CTb injections we found a bilateral population of labeled cells in the Pulc (Pulc-tectal neurons), which features a characteristic fusiform and multipolar morphology. In addition we performed immunohistochemistry for glutamate decarboxylase (GAD67) and neuropeptide Y (NPY), finding cells immunopositive for both proteins in the Pulc that closely match the spatial distribution and morphology of Pulc-tectal neurons. Notably, these cells form a continuous with neurons in the pretectum that are known to project to the SC and to express GAD67 and NPY as a neurochemical stamp. Interestingly, in birds there is a well define pretectal structure, the nucleus Pretectalis, that features morphological, hodological and neurochemical characteristic that closely correspond to that of the Pulc-tectal cells described here. Hence we speculate that these Pulc-tectal neurons are indeed migrated cells of pretectal, and not thalamic, origin, and correspond homologically to the cell population that form the avian nucleus Pretectalis. This speculation, if confirmed, would account for the oddity of what appears to be a descending projection from a dorsal thalamic nucleus to the SC.

PERIPHERAL EFFECTS OF AUDITORY-CORTEX MICROSTIMULATION IN THE OLIVOCOCHLEAR REFLEX STRENGTH IN THE ALPHA-9 KNOCK-OUT MICE

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The auditory efferent system comprises descending projections from the auditory cortex to the cochlear receptor, including the olivocochlear system, which is a mandatory pathway to the sensory epithelium. The olivocochlear reflex can be activated by contralateral acoustic stimulation, suppressing bilateral cochlear responses. Here, we measured the effects of contralateral noise (CN) in auditory brainstem responses (ABR, Waves I to V), previous, during and after auditory-cortex microstimulation (MS) (1 to 4 μ A, 32 Hz rate) in anesthetized *wild type* (WT) mice and in the $\alpha 9$ nicotinic receptor *knock out* (KO) mice, in response to tones of different frequencies (10-20 kHz). The latencies of cortical evoked potentials varied between 7 and 34 ms (WT) and from 8 to 22 ms (KO). In ten experiments (5 WT and 5 KO) auditory-cortex MS produced an increase of the suppressive effect of contralateral noise stimulation in wave I and V of the ABR. Larger effects were accompanied of auditory-cortex increased latencies in both cases (WT and KO). The difference between the effect of contralateral noise without cortical MS and with cortical MS was 0.6 to 6.5 dB in wave I and 1.5 to 10 dB in wave V in WT mice compared to KO mice which was 0.5 to 5.9 dB in wave I and 0.9 to 7.1 dB in wave V. These results suggest that the activation of efferent projections from the auditory cortex to subcortical nuclei, enhances the strength of the olivocochlear reflex on ABR responses.

ANATOMICAL AND PHYSIOLOGICAL EVIDENCE FAVORS A COLUMNAR ORGANIZATION FOR THE AVIAN VISUAL TELENCEPHALON.

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The sensory flow in the bird telencephalon has long been regarded as mostly linear. This means, primary pallial sensory areas generate projection towards secondary or tertiary order pallial structures without intrinsic circuitry. In contrast, the mammalian cortex has two prominent features: lamination of characteristic neuronal types (including primary sensory neurons), and radially arranged projections between cortical layers, forming anatomical and physiological columnar modules. The difference in organization of mammal's pallium and bird's pallium has been questioned by recent studies. These studies have shown that the visual sensory pallium is composed of three differentiated, layers: internal (Entopallium, E, thalamo-recipient), intermediate (Intermediate Nidopallium, NI, efferent,) and external (Mesopallium, M, associative), highly interconnected between them by a system of dorso-ventrally oriented, discrete and homotopic columnar bundles of axons. In addition, it has also been shown that the birds' Entopallium and Ni-M share molecular identity with cortical layer 4 and layer 2/3, respectively. In the case of the avian visual pallium, the detailed morphology of the cells and processes composing the columns, as well as the physiological operation of them, has not been investigated in detail. We have addressed these issues practicing intracellular cell fillings in chick brain slices, and current source density analysis(CSD) in anesthetized pigeons. Our results confirm that the neuronal axonal processes connecting these three layers are mostly dorso-ventrally oriented. Characteristic "column-forming" cell types of each layer were identified, including cells in the E and Ni projecting to the basal ganglia. CSD maps elicited by the electric stimulation of discrete E loci show a layered/sequential arrangement of synaptic activation, with characteristic sinks in each layer. Finally, local electric E stimulation elicited at the M spike activity restricted to the columnarly homotopic locus. These results strongly support a columnar organization for the avian visual pallium.

CONSPICUOUS FEATURES IN THE VISUAL SYSTEM OF A BASAL BIRD, THE CHILEAN TINAMOU (*NOTHOPROCTA PERDICARIA*)

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Extant birds diverged from a common ancestor during the Cretaceous period, probably over 100 mya, where they split into two grand clades, Palaeognathae (flightless Ratites and flying Tinamous) and Neognathae (all others). Because the Palaeognathae have been vastly ignored by comparative neurobiology, we started a research program focused on the visual system of a small Palaeognath, the Chilean Tinamou *Nothoprocta perdicaria*. By injecting neuronal tracers and using immuno-histochemical methods, we found that the Tinamou's retinal projections generally represent a phylogenetically conserved pattern common with Neognathous birds. However, some conspicuous features stand out from the neuroanatomy shared with Neognathae: a retinal projection transcending layer 7 into layer 8 of the optic tectum; a projection to deep tectal layers 11-13, traceable from the retina; and a large number of retrogradely labeled centrifugal neurons in the isthmo-optic region, which do not form a distinguishable nucleus, but rather a cluster of "ectopic cells". Interestingly, both conspicuous projections to the tectum have been described in chicken embryos as transient projections that disappear before hatching, suggesting that they represent ancestral characters. Likewise, the diffuse isthmo-optic nucleus may represent the link between the well-defined ION of most neognathous birds and the diffuse arrangement of centrifugal neurons of crocodiles, the closest living relatives to birds. Our findings stress the importance of the comparative neurobiological approach and call for future studies in Palaeognathae as an outgroup to common neognathous model species.

ON THE INFLUENCE OF NATURAL IMAGES SECOND ORDER STATISTICS IN THE RETINAL POPULATION CODING

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The retinal response from the *Octodon degus* (degu) rodent was assessed using multi-electrodes (252) arrays using natural stimuli obtained from their habitat, preserving in the stimuli (a movie) natural locomotor exploration and related point of view obtained using a mobile robot having a high definition digital camera. In particular we have studied the response of retinal ganglion cells (GC) when stimulated with sequences of natural images recorded using the robot that we have developed, from where we asked whether second order statistics are influencing the population responses, what is still an unsolved topic in the study of the visual system and we expect that some GCs will be preferentially tuned to natural statistics. Recorded GCs were classified according to their receptive fields, estimated through *spike-triggered* average analysis, where we found ON and OFF GC types in a 1:4 proportion, respectively. GCs were separated in different populations, their spiking activity was modeled using a spatio-temporal Gibbs distribution, derived from the maximum entropy principle, for different stimuli with different statistical properties: i) checkerboard, ii) natural movie and iii) natural movie with randomized phase. Having the Gibbs distribution that better match each population, we found significant differences between the responses to the different type of stimulus.

ROLE OF DOPAMINE RECEPTORS IN AROUSAL-INDUCED TASTE NEOPHOBIA

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Dopamine (DA) is an important endogenous catecholamine within the central nervous system, which binds to specific receptors in neurons and astrocytes and it plays a key role in the control of locomotion, learning, cognition and emotion. Current evidence suggests a role for dopamine in stress responses and anxiety-related symptoms. Understanding the role of dopamine in stress and anxiety may allow the future development of novel approaches to treat anxiety-related disorders. Therefore, we investigated the role of different dopamine receptors in the reaction to arousal-induced experiences, using arousal induced taste neophobia. Male rats were chronically implanted with cannulae into the insular cortex and tested for neophobia, using saccharin 0.1% as a novel taste presented in a high arousal context (HA; novel cage) or in a low arousal context (LA; homecage). Dopamine agonists and antagonists were injected into the insula or administered orally 10 minutes before taste presentation. Systemic Haloperidol (dopamine antagonist) decreased arousal-induced neophobia, effect that was blocked by intra-insular dopamine agonists. Furthermore, intra-insular D5 antagonist infusion decreased neophobia in HA. Our data indicate that specific Dopamine receptor types may be involved in arousal induced neophobia acting at the insular cortex.

EL CONTROL DE LOS DEDOS DE UNA MANO ROBOT MEDIANTE LAS SEÑALES MÚSCULARES DE DEDOS HUMANOS

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Estamos desarrollando una mano robótica y una interfaz de electromiograma como plataforma educativa para enseñar a alumnos cómo funciona la robótica, las señales del cuerpo, y las neuroprótesis. Tenemos un amplificador de cinco canales para aumentar la señales eléctricas de los músculos individuales del antebrazo; este amplificador es un “shield” para el popular microcontrolador “Arduino”. Con este microcontrolador controlamos los servomotores de los dedos de la mano. Tanto la mano como el amplificador son código abierto y fáciles de armar. Ahora los desafíos son los algoritmos de control: hay mucha superposición de las señales entre el dedo índice, el del medio, y meñique (los otros dos, no tanto). Podemos controlar 3 dedos, estamos investigando cómo mejorar las reglas para controlar cada dedo de manera independiente y eficaz.

PARALLEL ORGANIZATION OF THE DESCENDING PROJECTIONS FROM THE ARCOPALLIUM IN PIGEONS (*COLUMBA LIVIA*)

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The Arcopallium (Arc) is a large, heterogeneous pallial region in the caudo-ventral telencephalon in birds. The dorsal and intermediate Arc receive inputs from several sensory modalities, such as, auditory, trigeminal and visual. In addition the Arc sends prominent descending projections to several thalamic, brainstem and mesencephalic regions, including the main nucleus of the ascending tectofugal pathway, the optic tectum (TeO). While auditory and trigeminal pathways have been tracked to the arcopallium, the arcopallial areas receiving tectofugal visual inputs have not been determined. In this work we charted, electrophysiologically, the arcopallial areas displaying tectofugal visual responses and, by using anterograde and retrograde neural tracers, we traced the descending projections to subpallial targets, in particular to TeO. We found consistent tectofugal visual responses in the dorsal and the intermediate areas of the Arc, overall similar to those recorded at earlier tectofugal stages. PHA-L injections into these areas showed a massive projection to the deep tectal layers and to the brain stem, conspicuously sparing auditory and trigeminal targets. Conversely, PHA-L injections into the medial intermediate Arc labeled fibers in auditory regions in the thalamus and mesencephalon, and not in the TeO. In addition to this global parallel organization, the Arc descending projection to the tectum also maintains the dorsal-ventral segregation of the ascending tectofugal pathway. These results emphasize the segregated organization of the arcopallial connectivity, showing, in addition, that the intermediate Arc provides a top-down feedback to the tectum that is causally linked to the ascending tectofugal visual activity.

B SUBUNIT MODIFIES THE TOTAL GATING CHARGE MOVEMENT IN BK CHANNELS

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Large conductance Ca^{2+} - and voltage- activated K^{+} channel (BK) controls the membrane potential in most mammalian tissues, due to its nature of integrating-node of a large variety of intracellular signals. The α subunit can form complexes with β modulator subunits in different cell types. Recently, we showed that β -subunits ($\beta 1$ - $\beta 4$) modify the channel behavior stabilizing the BK voltage sensor in the active conformation (Contreras et al, 2012). Despite the fact that steady state behavior of voltage sensor produced by each of the beta subunits has been well characterized, most of the conclusion obtained is based in kinetic models that lack of thermodynamic validity. This is due to it is unknown which is the total gating charges that one BK α subunit channel can move and how they are modulated by different β subunits. To determine whether β -subunits contribute to the gating charge of the channel, the total gating charge movement per channel was measured in the pore-forming BK α subunit alone and with the different β subunits. To evaluate the number of charges per channel, we measured in the same patch, the number of channels (N) by non-stationary noise analysis, and then we isolate the gating current by profusely perfusing the internal side of the macropatch with a K^{+} -free solution. We found that the total number of charges per channel was 4.4, 3.0 and 4.2 (e0) for BK(α), BK($\alpha/\beta 1$) and BK($\alpha/\beta 3b$) respectively. A possible interpretation of this slightly decrease of the total charges in the presence of $\beta 1$ is that beta subunit interacts with the voltage sensor in alpha subunit, decreasing the extend of voltage sensor displacement during channel activation.

THE SH3 DOMAIN OF B-SUBUNIT OF VOLTAGE-ACTIVATED CALCIUM CHANNELS CONTROLS CHANNEL EXPRESSION VIA A DYNAMIN-DEPENDENT MECHANISM

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Calcium entry through voltageactivated calcium channels (VACC) plays an essential role in the exocytotic release of neurotransmitters and hormones. VACC are multi-protein complexes containing a pore-forming subunit ($\alpha 1$) and various auxiliary subunits, among them the β -subunit. The β -subunit regulates VACC gating and inactivation, as well its intracellular trafficking, assembly and surface membrane expression. The β -subunit belongs to the membrane-associated guanylate kinase class of scaffolding proteins (MAGUK) that comprise two protein-protein interaction domains. One of them is a SH3 domain ($\beta 2a$ -SH3) that interacts with dynamin and promotes dynamin-dependent endocytosis of VACC in *Xenopus* oocyte. Here we found that $\beta 2a$ -SH3 also reduces VACC currents by 50% in bovine chromaffin cells. Such effect is reverted when the cells were co-injected with a recombinant peptide containing the recognition motif for SH3 domain-containing proteins in dynamin-1 (Dyn829-842), indicating the mechanism probably depend on a $\beta 2a$ -SH3/dynamin interaction. This mechanism also seems to depend on $\beta 2a$ -SH3 dimerization, since no effect was observed when a dimerization-deficient mutant C113A was injected. Finally, the fact that SH3 domains from other dynamin partners did not reduce VACC currents as the $\beta 2a$ -SH3 does, suggest that a specific regulatory role of the β -subunit on VACC endocytosis.

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VOLTAGE SENSOR IMMOBILIZATION IN CALCIUM CHANNELS BY REM GTPASE.

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Voltage-dependent calcium channels (Ca_v) are the main pathway for calcium influx into cells, couple electrical signals to chemical stimuli that regulate from muscle contraction to gene expression. Ca_v are also the target of regulation by intracellular signals such as calmodulin, protein kinases and G protein. The subfamily of small GTPases similar to RAS (RGK; Rad/Rem/Gem/Kir), has been identified as a potent inhibitor of Ca_v . Specifically Rem act through different mechanisms that decrease calcium current: i) removal of Ca_v by enhancing dynamin-dependent endocytosis; ii) decrease the open probability of the channel; iii) immobilization of the voltage sensor channel domains. The mechanism underlying Ca_v voltage-sensor immobilization by RGK proteins is unknown, but a direct interaction of RGK proteins with functional domains of the channel has been suggested. Here we evaluate the interaction between Rem and the pore-forming subunit of a subtype ($\text{Ca}_v1.2$) voltage-dependent calcium channels using oocytes of *Xenopus laevis* as an heterologous expression system. Combining electrophysiological and single oocyte chemiluminescence methods, we found that co-expression of Rem with Ca_v reduces the maximum gating charge movement without changing the density of channel protein at the surface indicating that Rem decrease calcium current by immobilizing the voltage sensor rather than removing channels from the plasma membrane. Furthermore, the immobilization of $\text{Ca}_v1.2$ voltage sensor by Rem does not depend on the co-expression of $\text{Ca}_v\beta$, unlike in mechanism I and II, indicating that RGK GTPase interact with Ca_v pore-forming subunit. Our next aim is follow the movement of individual VSD using voltage clamp fluorometry (VCF).

PROXIMAL N-TERMINAL DOMAIN IS INVOLVED IN COLD AND MENTHOL SENSITIVITY OF TRPM8 ION CHANNEL

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TRPM8 is the main molecular entity responsible for detection of cold temperatures in the somatosensory system. This polymodal calcium-permeable cation channel is activated by cold, cooling compounds such as menthol and voltage. Among different orthologs of this channel, chicken TRPM8 (cTRPM8) displays larger sensitivity to cold and menthol compared to mouse TRPM8 (mTRPM8), suggesting that non-conserved regions could be able to tune the chemical and thermal sensitivity of the channel. Nevertheless, the molecular basis underlying these differences and the precise molecular mechanism involved in temperature sensing remained unknown. In order to identify structural domains involved in TRPM8 sensitivity to cold and menthol using orthologs, we performed sets of chimeras with TRPM8 from different species and other members of the TRP family. We evaluated the activity of these mutants using calcium imaging and patch clamp techniques in transfected HEK293 cells. We identify one region of 30 aminoacids in the proximal N-terminus that is involved in its sensitivity to cold and menthol. We found that the transference of this domain from cTRPM8 to mTRPM8 is sufficient to obtain a chimera with the characteristic features of the chicken ortholog, which include increased responses to cold and menthol, a 5°C shift in the temperature threshold to warmer temperatures, and a reduced EC₅₀ to menthol. Our results suggest a key role of the proximal region of the N- terminus in the fine tune of cold and menthol sensitivity of this polymodal ion channel.

THE B SUBUNIT N-TERMINUS IS INVOLVED IN THE MODULATION OF A-SUBUNIT VOLTAGE SENSOR OF BK CHANNELS

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BK channels are found in most mammalian tissues, from brain to liver to smooth muscle, where they could be modulated by specific auxiliary α subunits.

Recently, we showed that auxiliary $\alpha 1$ and $\alpha 2$ subunits stabilize the BK voltage sensor in the active conformation, and $\alpha 3$ has no effect on voltage sensor equilibrium. Despite the fact that the BK phenotype produced by each of the beta subunits has been well characterized, controversies exist regarding the molecular mechanisms by means of which these auxiliary subunits can modify the gating of BK channel. To identify the molecular determinants that confer to the $\alpha 1$ the ability to modulate the voltage sensor of BK channels, we constructed fifteen chimeras of $\alpha 1/\alpha 2$ and $\alpha 1/\alpha 3$ subunits by exchanging the N- and C-terminus, the transmembrane (TM) segments, and the extracellular loops, between them. Our results show that the cytoplasmic segments of $\alpha 1$ are responsible for voltage sensor modulation in BK channel. To gain insight in to the molecular determinants of this modulation we constructed additional chimeras by sweeping the N or C terminus of $\alpha 1$ ($\alpha 1N\alpha 3$, $\alpha 3C\alpha 1$, $\alpha 3N\alpha 1$) and found out the N-terminal of $\alpha 1$ is the main region that modulates BK gating. The N-terminus contains a series of charged amino acids residues that can account for this modulation. In fact, neutralizing residues K3 and K4 by mutagenesis virtually abolished the effects of $\alpha 1$ on Q/V and the modulating effect of $\alpha 1$ is abolish when the ionic strength is decrease to 10 mM. These results suggest that $\alpha 1$ -dependent modulation of the BK voltage sensor is due to long-range electrostatic interaction. In conclusion, only $\alpha 1$ affects the BK channel voltage sensor and the charged residues in the cytoplasmic N-terminal are necessary and sufficient to recover the gating properties of $\alpha/\alpha 1$ channel phenotype.

IDENTIFICATION OF RESIDUES INVOLVED IN CX26 HEMICHANNEL SLOW GATING.

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The most well-known role of Connexins (Cxs) is to communicate the cytoplasm of two adjacent cells forming a gap junction channel in the apposition zone. On the other hand, Cxs form the so called "hemichannels", a fully functional voltage-gated non-selective ion channel, which present two gating mechanism called "slow" and "fast" gating. Hemichannel consist of 6 monomers, each one composed of four transmembrane domains. Despite the fact that hemichannel are voltage activated, it lacks classical voltage sensing domain described for canonical voltage-gated channels. Furthermore, the molecular determinants associated to the voltage activation in connexins hemichannels are still elusive. In this work we define which are the molecular determinants associated to voltage detection in human Cx26 hemichannels. Using two electrode voltage-clamp in *Xenopus laevis* oocytes, we study how the steady-state conductance/voltage (G/V) relationship is affected by the neutralization of different charged residues located within the first transmembrane domain. We have found that hCx26 G/V presents a $z\beta$ of 1.4 e_0 for the slow gating mechanism. Our data shows that neutralizing K41 residue (K41N) increases voltage dependency from 1.4 to 2.5 e_0 . We are able to determine quantitatively the voltage dependence of hCx26 wt hemichannels, and for the first time we found a charged residue associated to voltage activation of the slow gating.

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UNRAVELING THE DUAL ROLE OF DOPAMINERGIC SYSTEM IN DROSOPHILA OLFACTORY AND MOTOR RESPONSES

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Dopamine (DA), a well-known biogenic amine, contributes in *Drosophila* to the modulation of Mushroom Body (MB) activity, a CNS integration center for several sensory stimuli that has been also associated to motor responses. Here we studied the role of different DArgic clusters projecting to MB on the behavioral responses to an aversive odorant stimulus (Benzaldehyde, Bz). We expressed tetanus toxin (Tetx) or the potassium channel Kir2.1 in DArgic clusters to block DA release or activity. We recorded adult fly behavior in absence and presence of Bz in a circular arena and measured Activity Time (AT) and Preference Index (P.I.), as measures of motor and olfactory behaviors, respectively. Our results show that two DArgic clusters (PAM and PPL1) differentially modulate AT and P.I. In one hand, blocking activity of PPL1 with Kir2.1 increases P.I. without affecting AT. On the other hand, the expression of Tetx in PAM neurons (PAM/Tetx) decreases AT and P.I. A treatment with Nicotine, a drug that increases motor activity in flies, restores the AT defect in PAM/Tetx flies without affecting P.I. suggesting that it is possible to dissect out and manipulate the two components of the behavioral effects observed in PAM/Text flies. These results suggest that PAM and PPL1 have different effects on olfactory and motor responses.

BK CHANNELS ACTIVATION BY 17 β -ESTRADIOL IS ASSOCIATED TO VOLTAGE SENSOR MODULATION THROUGH DIRECT BINDING TO β 1 AUXILIARY SUBUNIT

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BK channels are involved in the physiological regulation of vascular smooth muscle contractility and blood pressure. 17 β -Estradiol (E2) acts as a protecting factor in the vascular tissue, modulating the BK channel, causing a membrane hyperpolarization and decreasing the vasoconstriction. Although the mechanism by which β 1 is modulating BK channel has not been completely described, the accessory β 1 subunit is necessary for this modulatory effect. Our aim is to identify the binding site for E2 and the molecular elements involved in the modulation of BK channel by E2. Binding assays in HEK293 cells transfected with BK α -pore forming subunit alone or in combination with β 1, were carried out with a probe of E2 (E2-BSA-FITC). The distribution of E2-BSA-FITC was monitored by confocal microscopy, revealing that E2 binds to β 1 subunit. Additionally, we express α and β 1 subunits in *Xenopus laevis* oocytes and record gating currents (I_g) in inside-out patch clamp in presence of E2. Our results show that E2 modifies the charge stabilization of the voltage sensor domain (VSD) in BK channel only in presence of β 1, decreasing the V_h for the charge versus voltage (Q/V) curves. Thus E2 in the presence of β 1, changing the resting-active equilibrium of the voltage sensor in BK channel, suggesting that it is able to modulate BK channel through the auxiliary subunit. The molecular mechanism for this modulation remains to be determined.

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ANALYSIS OF OSCILLATORY RESPONSES IN THE OLFACTORY SYSTEM OF RAINBOW TROUT

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In this study, we aboard the analysis of signal processing in the olfactory system of the rainbow trout (*O. mykiss*) with parallel extracellular recordings of the electroolfactogram (EOG) and micro-electroencephalogram (mEEG) of olfactory processing centers in the forebrain to answer: Where are olfactory field potential oscillations generated? Which are their basics features? Is there phase synchrony between different olfactory sectors? Field potential oscillations in response to diverse olfactory stimuli were observed in the entire olfactory bulb, and in the areas Vv and Dp of the telencephalon, but contrary to prior reports they were absent from the olfactory epithelium. Our results show that the olfactory bulb, Vv and Dp are in phase with frequencies around 9 Hz during the olfactory response, suggesting a synchronization of olfactory processing centers in the forebrain. These oscillations correspond to the frequency band denominated “beta” in mammals, which normally activates in response to odorants and is related to olfactory learning and alertness.

DOPAMINE D2 SHORT RECEPTOR INCREASES K-OPIOID RECEPTOR LOCALIZATION IN THE PLASMA MEMBRANE

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Dopamine D2 short receptor (D2S) and κ -opioid receptor (KOR) have an inhibitory control on dopamine release at the presynaptic level in the nucleus accumbens, a brain area related to reward function. Behavioral studies have shown that co-activation of KOR with the selective KOR agonist U69593, and D2 receptor with the selective D2 receptor agonist quinpirole (QNP) at pre-synaptic doses, switches the effect of D2S activation from locomotor depression to locomotor activation. In addition, previous studies from our laboratory have shown that D2S receptor induced-regulation of dopamine extracellular level is impaired in the nucleus accumbens of rats exposed to repeated administration of U69593. Taking together, the data suggest a functional interaction between KOR and dopamine D2S receptors. We used heterologous expression of Flag-D2S receptor, HA-KOR, or both in PC12 cells and quantitative analysis of double immunofluorescence confocal images to analyze if co-expression of D2S and KOR changes the localization of D2S receptor in the plasma membrane. In this study, we show that Flag-D2S co-localizes with Wheat Germ Agglutinin (WGA), marker of plasma membrane, in cells expressing Flag-D2S alone. In contrast, HA-KOR is primarily localized intracellularly when expressed alone. In cells expressing both receptors, there is no difference in Flag-D2S localization in the plasma membrane, but HA-KOR co-localization with WGA increases. These data indicate that D2S-receptor changes the localization of KOR increasing its presence in the plasma membrane.

THE BENEFICIAL EFFECT OF ENVIRONMENTAL ENRICHMENT ON RETT SYNDROME-LIKE PHENOTYPE IS ASSOCIATED TO A CELLULAR ARCHITECTURE RECOVERY AND REESTABLISHMENT OF GLUTAMATE-RELATED GENE EXPRESSION.

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Rett syndrome (RTT) is a severe neurodevelopmental disorder and one of the leading causes of mental retardation in girls. The symptoms exhibited by RTT patients include autistic features, motor and respiratory abnormalities, autonomic dysfunction and anxiety alterations.

Previously, our and others labs demonstrated that the phenotype exhibited by RTT mouse models is reversible and that environmental enrichment (EE), a widely used paradigm to increase synaptic plasticity, is a plausible alternative to prevent the neurological alterations associated to RTT. To determine the molecular and cellular mechanisms underlying the beneficial effects of EE on the RTT-like phenotype, we exposed an RTT mouse model to permanent EE or control conditions since weaning.

Our results showed that the permanent exposition to EE was effective attenuating the progression of locomotor alterations, motor coordination and anxiety-like behavior exhibited by an RTT mouse model. We also found that body weight, neurological damage and lifespan were reestablished by an enriched environment. This attenuated phenotype was accompanied by changes in the cellular architecture of motor cortex M1 and M2. To evaluate whether this morphological changes were associated to the reestablishment of glutamate homeostasis, we evaluated the expression of glutamate transporters and receptors. We found that EE partially reestablished the altered-gene expression pattern observed in this RTT mouse model.

In summary, the EE attenuates the RTT-like phenotype and increases the lifespan of an RTT mouse model, almost certainly by reestablishing the cellular communication in the brain.

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SYNAPTIC VESICLE EXOCYTOSIS IN CELLS DERIVED FROM CEREBRAL CORTEX OF 16 TRISOMY MICE, AN ANIMAL MODEL OF DOWN SYNDROME

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Neurons from trisomy 16 (Ts16) mice, an animal model of Down Syndrome, as well as CTb cells (a cell line derived from cerebral cortex of Ts16 fetal mice), exhibit decreased fractional release of [3H]-acetylcholine. The mechanism underlying this impairment remains unclear. Here, we explored the possibility that altered exocytosis of synaptic vesicles is responsible of such cholinergic dysfunction. To monitor exocytosis, we expressed the vesicular acetylcholine transport linked to pHluorin in CTb and CNh cells (a cell line derived from a normal littermate), and measured single exocytotic events with total internal reflection fluorescence microscopy.

In resting conditions, both cell lines exhibit exocytotic events with fluorescence decay kinetics of less than 2 s. These decay kinetics are slower when the cells are treated with 100 mM HEPES or 100 nM bafilomycin, a vesicular ATPase inhibitor. Both agents slow the acidification of recycled vesicles after fusion pore closure, yet they do not affect vesicles that collapse with the plasma membrane. Hence, these results suggest that the main mechanism for release of vesicular content in both cell lines is a “kiss and run” exocytosis. The decay kinetics of the exocytotic events was also slowed down after the treatment with actin polymerization inhibitors, wiskostatin or cytochalasin D, indicating that actin polymerization modulates the duration of this events in both cellular lines. These results indicate that, under resting conditions, both cell lines release their vesicular content by a “kiss and run” exocytosis mechanism that is highly regulated by cortical actin cytoskeleton.

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MICROTUBULE ASSOCIATED PROTEIN 1B (MAP1B) REGULATES THE MORPHOLGY AND PHYSIOLOGY OF PRESYNAPTIC TERMINALS IN VITRO

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Microtubule-associated protein 1B (MAP1B) is expressed predominantly during the development of mammal nervous system. However its expression persist in adult stages where it modulates synaptic processes. In this work we analyze the role of MAP1B in presynaptic terminals. MAP1B is expressed in mice adult brain and in mature neurons in vitro where interacts with the presynaptic protein Snapin. Mature MAP1B ^{-/-} neurons present a delay in the kinetic of neurosecretion compared to WT neurons. 3D reconstruction analyses using Imaris Bitplane software reveals a decrease in the density of both presynaptic and postsynaptic terminals, and also a decrease in the number of synaptic contacts. In neurons lacking MAP1B there is an increased proportion of mislocalized presynaptic terminals, which could correspond to orphan presynaptic sites. Ultrastructural analyses from 21 days in vitro (DIV) cultured neurons show a decrease in the synapse density and an increased proportion of immature synapses in MAP1B deficient neurons. Finally there is an altered phenotype in presynaptic terminals of MAP1B ^{-/-} neurons, showing a reduction in the density of both the synaptic vesicles (SV) and of the synaptogenesis related-dense core vesicles (DCV). These results led us to propose MAP1B as a key regulator of the establishment of synaptic contacts and of the morphology and functionality of presynaptic terminals in vitro.

PIASG MEDIATED REPRESSION OF NURR1 DEPENDS OF ITS INTERACTION WITH THE AF-1 AND AF-2 DOMAINS

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Nurr1 is a transcription factor with major expression in the central nervous system, involved in the phenotype differentiation and survival of the midbrain dopamine neurons. Since Nurr1 is an orphan nuclear receptor lacking a ligand, it is important to reveal its regulation by posttranslational modifications and partner's interaction. Nurr1 has three main domains: the activation function (AF)-1 domain, variable in the family, a conserved DNA binding domain and the AF-2 domain that encompasses the putative ligand binding domain. Previously, we found that PIASg represses Nurr1 transcriptional activity and is capable of binding *in vitro* to both AF-1 and AF-2 domains of Nurr1. We propose that PIASg forms a homodimer to bind both Nurr1 AF domains simultaneously. To demonstrate our hypothesis, we created Nurr1 variants expressing the AF-1 or the AF-2 domain and assayed them in competition analyzes. Using a mammalian reporter gene assay, we show that the overexpression of AF-1 or AF-2 Nurr1 domains relieves PIASg repression on Nurr1 transcriptional activity. Co-immunoprecipitation assays using two different PIASg epitope-tagged recombinants showed that PIASg does not homodimerize in HEK293T cells. Ongoing experiments are performed to test whether PIASg homodimerization may occur in other cell types or the presence of increasing amounts of Nurr1.

COORDINATED INTERACTIONS BETWEEN DORSAL HIPPOCAMPUS AND MIDLINE THALAMUS DURING NETWORK OSCILLATIONS

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The midline thalamus is reciprocally connected with most of the medial temporal lobe, including the hippocampus and entorhinal cortex, likely interfacing communication with other cortical and subcortical territories. Here, we report the modulation of thalamic activity by hippocampal pathways and functional homogeneity of anatomically identified midline thalamic neurons during network oscillations in anesthetized mice. Indeed, hippocampal theta oscillations faithfully entrained the discharge activity of over half of thalamic neurons; even though the thalamus displayed prominent delta oscillations, which seemed to be volume-conducted from the medial prefrontal cortex. Additionally, sharp wave-ripples episodes in the hippocampus were followed by discrete bursts of thalamic activity in the gamma band. Anatomically identified thalamic neurons commonly expressed calretinin or calbindin in their somata, with calretinin-positive neurons discharging at lower rates than calretinin-negative neurons, irrespective of the coexpression of calbindin; thus suggesting an incipient neuronal diversity in the thalamus. Our results indicate that the midline thalamic projection system comprises relatively homogeneous neuronal populations, which are differentially modulated by hippocampal pathways during network oscillations, a fact that may be instrumental for context-guided learning and memory encoding during active exploration, as the thalamus is anatomically located in a pivotal position to interface the dialogue with cortical circuits required for memory specificity and generalization.

TARGETING ASTROCYTES IN THE TREATMENT OF ANXIETY AND DEPRESSION

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Most drugs used in psychiatry modulate neuronal synapses. However, recent studies suggest that astrocytes release transmitters into the synapse (known as gliotransmitters) including glutamate, ATP, glycine and d-serine, which are required for synaptic plasticity. One of the mechanisms by which this release occurs is via functional hemichannels that do not form gap junctions. We wish to prove that astrocyte hemichannels (formed by Cx43, Cx30 and pannexin 1) may become a target for treating two of the most common psychiatric disorders; depression and anxiety.

Using bioinformatics, we designed mimetic peptides able to open functional hemichannels without affecting gap junctions. The effectiveness of the peptides was determined by dye uptake and dye coupling essays. The peptides were micro injected into the ventral hippocampus in adult male rats implanted with chronic cannulas and their effects on anxiety-like symptoms were measured using the Open Field and Dark/light exploration tests and on depressive-like symptoms using tail suspension test (TST) and forced swim test (FST).

Mimetic peptides that modulate connexin hemichannel opening without affecting gap junction activity were able to reduce anxiety-like and depressive-like symptoms in rats. Thus, present evidence suggests that astrocytic hemichannels could be used as novel targets for drugs treating psychiatric disorders.

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A CRITICAL PERIOD FOR SYNAPTIC PLASTICITY IN THE RAT OLFACTORY AMYGDALA

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One of the cellular mechanisms underlying memory formation is long-term potentiation (LTP), a form of synaptic plasticity. The amygdala anterior cortical nucleus (ACo) is a three-layered structure that receives direct input from the olfactory bulb via the lateral olfactory tract (LOT) and has been linked to olfactory emotional learning. We assessed the induction of LTP during the first month of postnatal life in the LOT-ACo connections and investigated its regulation by olfactory experience in rats. Field synaptic potentials were recorded in brain slices from 6 to 34 days-old animals. Significant LTP induced by presynaptic theta-burst stimulation was observed at P11-15 (~15%), P16-20 (~26%) and P21-25 (~32%). However, around the end of the first postnatal month (P26-34), the LTP induction protocol failed to produce strengthening. A possible modulation of plasticity by sensory experience was evaluated by olfactory deprivation through the occlusion of one nostril. We did not observe differences in basal transmission between the hemispheres ipsi and contralateral to deprivation, suggesting a homeostatic compensation. However, significant potentiation was induced in both hemispheres at P26-34, in contrast to naïve animals. Our results demonstrate the existence of a critical period for the induction of LTP in the olfactory afferents to the amygdala. This means that only during a postnatal time window is it possible to induce synaptic potentiation. The critical period starts at early ages (P11-15) and closes at the end of the first month. Our results also suggest that this property depends on olfactory experience, as sensory deprivation extends the critical period.

ANTI-STRESS EFFECT OF THE CANNABINOID RECEPTOR TYPE 1 ANTAGONIST (AM251) IN SPRAGUE-DAWLEY RATS

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Introduction: Endocannabinoid (eCB) system modulates the neuronal activity of amygdaloid complex by the type 1 cannabinoid receptor (CB₁). This brain area regulates anxiety and corticosterone levels, the major stress hormone. On the other hand, chronic stress increases the eCBs levels in the amygdala, as well as anxiety and plasma corticosterone levels.

Objective: The aim of this study was to evaluate the effects of AM251 on anxiety and plasma corticosterone levels in the stressed rats.

Methods: Male Sprague-Dawley rats were subjected to chronic restraint stress (21d/6h); control animals were not exposed to any type of experimental stress. Both groups were treated with vehicle (i.p., physiologic serum) or AM251 (i.p., 0.3 mg/kg/day). Afterward, locomotor activity and anxiety were evaluated in the open field test. Corticosterone levels were quantificated by ELISA in blood samples.

Results: Stressed rats treated with AM251 had lower levels of anxiety and plasma corticosterone compared to vehicle-treated animals. Conclusions: These results demonstrate that AM251 treatment had a strong anti-stress effect in the rats.

EVIDENCE FOR A SENSITIVE PERIOD ON METAPLASTIC CHANGES INDUCED BY METHYLPHENIDATE IN THE RAT PREFRONTAL CORTEX

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Methylphenidate (MPD) is extensively used therapeutically in children and adolescents suffering from Attention Deficit/Hyperactivity Disorder. Its influence on learning and academic performance, however, is disputed.

We studied the effects of MPD on learning and synaptic plasticity using a radial maze test and induction of LTP in the prefrontal cortex in vivo. Rats (PND 42) were tested in the radial maze for 15 consecutive days after having received injections ip of 0, 0.2, 1 and 5 mg/Kg each day of testing. Without further administration of MPD, long-term potentiation was induced two weeks after the last injection of MPD by electrical stimulation of the callosal commissures and recorded in the prefrontal cortex (L: 2,5; A: 5,0 mm). Times to complete the task in the maze were reduced at 1 mg/Kg, but increased at 5 mg/Kg.

LTP in the prefrontal cortex two weeks after the last MPD injection was strongly increased in the groups that had received 1 or 5 mg/Kg (from 20 to 80%, approx.), but was not significantly changed in the 0.2 mg/Kg group. In contrast, in another group of rats that received exactly the same treatment except for starting of the testing/injections one week later (PND 49), LTP was undistinguishable from controls.

We conclude that:

- Plasticity changes as reflected in LTP modulation may be a factor in learning improvement.
- MPD-induced metaplasticity lasts for at least two weeks.
- It must be induced not much later than in the sixth week indicating the existence of a sensitive period.

FONDECYT 1120580 (BM); DICYT 020993Z (MZ); FONDECYT 1120952 (AH); DICYT 021401SB (PSB)

THE EXPRESSION OF THE D2 DOPAMINE RECEPTOR IS ALTERED IN A RAT MODEL OF OBSESSIVE-COMPULSIVE DISORDER

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Obsessive-compulsive disorder (OCD) is a chronic neuropsychiatric disease with high genetic influence and 1-3% prevalence worldwide. Changes in neurochemical processing in OCD are not entirely clear; however, evidences indicate alterations in the dopaminergic system. Repeated injections of Quinpirole (QNP), an agonist of the dopamine D2 receptor (D2R), induce locomotor sensitization and compulsive checking behavior in rats, constituting an animal model of OCD. Interestingly, the co-administration of the kappa opioid receptor agonist, U69593 (U69), potentiates QNP-induced locomotor sensitization. The aim of this study is to quantify mRNA and protein levels of the D2R in nigro-striatal and mesolimbic pathways in this rat model of OCD. Rats were repeatedly treated with QNP and U69 (8-10 injections). Total RNA from each brain nuclei was extracted 2- or 48 hrs after the last injection and RT-PCR with specific primers were used to amplify the long and short isoforms of D2R. Whole protein extracts were obtained 48 hrs after the last injection and processed to quantify each isoform of D2R level. Preliminary results show that both D2R mRNA isoforms decrease in dorsal striatum of QNP treated rats, effect abolished with U69 co-administration. In contrast, U69 potentiates QNP effect in the nucleus accumbens and ventral tegmental area. D2R-like bands at expected size (~ 50kDa) were detected from all nuclei. Taken together, the data suggest that repeated stimulation of D2R induces specific changes of its expression in the nuclei of the reward circuit, which may underlie compulsive behaviors.

BEHAVIOURAL AND GABAERGIC IMPAIRMENT IN A RAT KETAMINE MODEL OF SCHIZOPHRENIA

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Chronic ketamine (Ket) administration has been widely used as an animal model of schizophrenia, reproducing both, the cellular changes and cognitive impairment that characterizes to this syndrome. Nevertheless, there are few evidences about modifications on GABAergic synaptic transmission in the main structures related to working memory, including prefrontal cortex and hippocampus. In order to assess how chronic Ket-treatment affect the GABAergic transmission of hippocampal formation, male *Sprague-Dawley* rats were daily-injected with Ket (i.p.; 30 mg/kg; seven days) or Vehicle (NaCl 0.9%) and used for behavioural tasks and electrophysiological recordings. Ket-treated rats increase both, total travelled distance and anxiety, whereas the social contact time was diminished. However, we found no differences between groups on spatial working memory, which was measured by spontaneous alternation task. Intracellular recordings (whole cell) of CA1 pyramidal cells from hippocampal slices of Ket-treated rats showed lower amplitude of both spontaneous and miniature inhibitory postsynaptic currents (sIPSCs and mIPSCs; respectively) than vehicle group (87.3 ± 19.2 and 57.1 ± 9.0 pA for Ket-group and 130.9 ± 19.8 and 74.5 ± 14.8 pA for Veh-group, respectively). Both sIPSC and mIPSC frequencies as well as paired pulse index showed no differences between groups (Ket: $25.67 \pm 3.2\%$; Vehicle: $32.85 \pm 2.2\%$), ruling out possible presynaptic changes induced by Ket-treatment. Our results indicate that in this schizophrenia-model, hippocampal GABAergic transmission is post-synaptically diminished, lowering the inhibitory synaptic efficacy and leading a loss of excitatory/inhibitory balance required for working memory process.

AN AMPHIPATHIC ALPHA-HELIX IN THE N-TERMINAL OF CORTICOTROPHIN RELEASING FACTOR BINDING PROTEIN SERVES AS ITS SORTING SIGNAL TO THE REGULATED SECRETORY PATHWAY.

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Corticotrophin releasing factor (CRF) is a key player in the stress response activating the hypothalamic pituitary adrenal axis. CRF is also involved in the reinstatement of stress-induced drug seeking behavior. CRF binding protein (CRFBP) is a 37-kDa glycoprotein that binds CRF with high affinity. CRFBP reduces plasmatic CRF levels during human pregnancy. It has recently been proposed that CRFBP facilitates CRF-induced activation of CRF-R2 receptors in the central nervous system. CRFBP enters the regulated secretory pathway; however, the sorting domain by which CRFBP enters to the regulated secretory pathway remains unknown. We used in silico tools to determine the putative sorting domain of CRFBP. We determined putative α -helical domains along CRFBP sequence using secondary structure prediction programs (GORV and NPS@ Consensus Secondary Structure Prediction) and structural modelling (ROBETTA 3D modelling web server). The helical wheel projection (PEPWHEEL) showed that the (50-74)-CRFBP α -helical domain has an amphipathic configuration, signature of other sorting domains. This domain is highly conserved among different mammalian species. Thereafter, we studied the subcellular localization and release behavior of chimeras of CRF-BP transfected in both HEK293T and PC12 cells. The predicted (50-74)-CRFBP amphipathic α -helical domain was capable of sorting a mutant form of proCART, without its sorting domain, to the regulated secretory pathway. The ProCart1-53CRFBP50-74-EGFPm chimera colocalized with secretogranin II and presented a subcellular localization associated to the TGN and secretory granules in PC-12 Cells. Thus, our results show that the amphipathic alpha-helix in the N-terminal of CRFBP is necessary for its sorting to the regulated secretory pathway.

INCIDENCE AND FUNCTIONAL CHARACTERISTICS OF TRIGEMINAL COLD-SENSITIVE NEURONS WITH PARADOXICAL RESPONSE TO HEAT.

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A fraction of the peripheral axons of somatosensory cold thermoreceptor neurons (CTNs), which fire with temperature decreases and silence when temperature rises to 37°-38°C, develop a new impulse discharge at 42-44°C, a phenomenon known as the paradoxical response (PR) to heat of CTNs. Signalling through these neurons could underlie the erroneous conscious sensations of cold and the heat-conserving autonomic and motor reactions that accompany high fever. Nevertheless, the neuronal phenotype of cold-sensitive neurons with PR and the molecular mechanisms underlying this phenomenon have not been clarified. Using focal extracellular recording of corneal CTNs, complemented with patch clamp recordings and Ca²⁺ imaging in trigeminal cultured neurons of adult mice, we have studied the incidence of the PR and the functional characteristics of CTNs innervating the cornea exhibiting PR. Interestingly, ~75% of corneal CTNs are sensitive to heat. Temperature thresholds distribution and firing pattern evoked by cold were not different between CTNs with and without PR. Trigeminal CTNs with PR to heat in culture show mean cold temperature thresholds and biophysical membrane properties undistinguishable from CSNs without heat sensitivity. Capsaicin sensitivity among CTNs, an activator of heat-sensitive TRPV1 channels, shows no direct correlation with their heat responsiveness. Our results suggest that PR is homogeneously distributed among the population of CTNs, and that the biophysical properties and chemical (capsaicin) sensitivity of neurons exhibiting PR are not different from those observed in canonical CTNs insensitive to heat.

BIOGENIC AMINES SYSTEMS CONTRIBUTE TO OLFACTORY RESPONSES IN *DROSOPHILA* LARVAE

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Introduction. It is well known that biogenic amines as dopamine and serotonin modulate behaviors ranging from motility to learning. In nature, the olfactory system plays an important role in the survival of individuals in search of food and preventing attacks of possible predators. We aim to identify the contribution of central biogenic amines systems in odor processing in *Drosophila* larvae. **Materials and Methods.** Wild type flies (wt) and animals expressing a mutation for the serotonin and dopamine transporters (SerT and DAT, respectively) were used. The response to a natural larval attractant, Benzaldehyde (Bz, 1%), as opposed to water was studied. **Results.** Compared to wt animals where a strong attraction is observed, SerT mutant larvae fail at responding to the odor stimulus, showing no preference when given the choice of Bz or water. In contrast, DAT mutants show a slight aversion to Bz. **Discussion.** Our results suggest that serotonergic pathways are involved in olfactory discriminatory behaviour. On the other hand, DAT results would argue in favor of the idea that dopaminergic pathways also contribute to olfactory responses, having an opposite effect. However, DAT mutants were generated in a different genetic background and we are currently evaluating whether this fact plays a role in our results.

INCREASED FUNCTIONAL EXPRESSION OF TRPM8 CHANNEL IN CORNEAL PRIMARY SENSORY NEURONS IN RESPONSE TO AXONAL DAMAGE

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Injury of the sensory fibers innervating the cornea is frequently followed by dysesthesias, altered tear production, and changes in thermal and chemical sensitivity. The molecular and cellular mechanisms underlying the alterations in the transduction capability of primary sensory neurons in this tissue in response to axonal damage are poorly understood. In the cornea, both the responses to cold and the ongoing electrical activity of the exquisitely temperature-sensitive cold thermoreceptor neurons (CTNs) are strongly dependent on the functional expression of the cold- and menthol-activated channel TRPM8. Corneal CTNs act not only as cold sensory neurons, but also as the humidity detectors of the ocular surface, and their role in the sensory alterations in response to axonal damage remains unclear. Using calcium imaging and electrophysiological recordings in retrograde labeled corneal neurons dissociated from trigeminal ganglia, we studied the modifications in thermal- and chemical-sensitivity of CTNs that result from the controlled injury of corneal sensory axons in mice. We found that surgical injury of corneal fibers results in an increase in the percentage of cold-sensitive neurons and in their sensitivity to the TRPM8 activators cold and menthol. These results suggest that altered cold sensitivity of the eye surface induced by surgical damage of corneal CTNs could be linked to an increase in the functional expression of TRPM8 channels in these sensory fibers.

EXPLORING EXOGENOUS COPPER ROLE ON EXCITABILITY IN RAT HIPPOCAMPAL SLICES WITH DIFFERENT ENDOGENOUS COPPER CONCENTRATIONS: 20 AND 60 DAYS OLD ANIMALS

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An endogenous neuromodulator role for copper in mammals has been considered given that: copper is synaptically released in some CNS regions, it modulate several voltage and neurotransmitter gated channels which are expressed in the hippocampus and in Menkes and Wilson's patients, the loss of copper homeostasis causes neurological symptoms. Nevertheless, the mechanisms by which it exerts its neuromodulatory effects have not been established in a functional network. Thus we chose the hippocampus to characterize copper's role and found that exogenously added nanomolar copper rises the excitability in the CA1 region of 20 days old rats. We also had preliminary evidence that copper content decreases in CA1 area between 20 and 60 days old rats. In this study we tried to assess if spontaneous discharges in CA1 are affected by age and if there is a correlation with copper content. We measured the spontaneous action potential rate in the CA1 region of hippocampal slices in basal condition and after adding copper in 20 and 60 days old rats. We found that: basal discharge rate was the same at these two ages, that 0.05 μ M added copper decreased the rate at 60 but not at 20 days, while 10 μ M augmented the rates at 20 but not at 60 days old rats. These results suggest endogenous copper sensitivity and ability to modulate the excitability changes through postnatal development, an aspect important to eventually understand the fine mechanism of copper related pathologies.

PANNEXIN 1 REGULATES BIDIRECTIONAL HIPPOCAMPAL SYNAPTIC PLASTICITY IN ADULT MICE

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Pannexin 1 (Panx1) is the most studied member of Pannexins family former of single membrane channels. In the brain, Panx1 is expressed in pyramidal cells showing a preferential distribution in postsynaptic sites where it colocalizes with scaffold proteins and glutamate receptors. Research on the synaptic basis for their postsynaptic localization indicates that Panx1 channels stabilize synaptic plasticity and is needed for learning. Although it has been suggested that Panx1 channels play a role in excitatory long-term potentiation (LTP), it remains unknown whether these channels also modulate long-term depression (LTD) or the balance between both types of synaptic plasticity. To examine the participation of Panx1 in synaptic plasticity we used hippocampal slice recordings in the Schaffer collateral-CA1 path from adult (6–12 months old) transgenic mice lacking Panx1 and age matched wild-type littermates. We found that the absence or the blockade of Panx1 channels enhances LTP whereas precludes the induction of LTD, modifying the threshold for the induction of excitatory synaptic plasticity in the hippocampus of adult mice. This modification could be due to GluN2 subunit composition of NMDA receptors (NMDAR) as we observed that the absence of Panx1 differentially modifies the contribution of GluN2A and GluN2B containing receptors to LTP and LTD. These findings indicate that Panx1 is a key player in the regulation of excitatory synaptic plasticity, controlling the proper traffic of synaptic receptors, and playing a crucial role in maintaining the balance between LTP and LTD.

MUTATIONS IN PROTEINS ASSOCIATED WITH PARKINSON DISEASES MODIFY INNATE BEHAVIOR IN *DROSOPHILA MELANOGASTER*

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Parkinson disease (PD) is a degenerative disorder of the central nervous system, which has been associated with movement-related symptoms. More than 96% of PD patients present some kind of olfactory dysfunction. Although the molecular mechanisms responsible for this disease are not clear it has been described that mutations in specific genes would be responsible for some familial PD cases. In this work we describe the behavioral effects induced in *Drosophila* by expression of mutants for two proteins previously associated with PD, α -synuclein and PTEN-induced putative kinase 1 (PINK1). Flies expressing the human wildtype or mutant (A30P) α -synuclein protein in dopaminergic neurons were used. In other experiments, we studied flies expressing a mutation for *Drosophila* PINK1. Single male or female flies were evaluated at different ages: 0-3; 7-10; 14-17; 21-24 and 28-31 days old. Flies were placed in a circular arena with two cottons in opposite sides. Behavior of each fly was recorded for 3min in absence or presence of benzaldehyde 1% by the Buridan Tracker software. Olfactory discrimination (OD) was evaluated as odor Preference Index (PI). Several motor parameters were also measured. We observe differences in PI between male and female flies. No effect in OD was observed in flies expressing mutant proteins. On the other hand, our results suggest that the expression of mutants for α -synuclein and PINK1 in *Drosophila* induce defects in several motor parameters, similar to PD-related symptoms. These data suggest that these mutations could affect olfaction and motor behavior through independent mechanism.

ON PERMEABILITY PROPERTIES OF PANNEXIN 1 HEMICHANNELS

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Pannexin 1 (Pax1) is a member of a protein family constituted by three members (Pax1-3). They present little homology to innexins and virtually no homology to connexins. In vertebrates, Pax1 is ubiquitously expressed and play critical roles in numerous physiological and pathological cell responses. Pax1 hemichannels are permeable to ions and small molecules including ATP but their permeability features remain controversial and require further characterization. They can be activated via purinergic receptors or membrane stretching. Here, we characterized several features of Pax1 hemichannels. HeLa parental cells (HeLa-P) and HeLa cells transfected with Pax1 were used. RT-PCR analyses revealed absence of Pax2 and Pax3. Hemichannels were activated by stretching induced by drops of extracellular saline solution. The cell uptake of 4',6-diamidino-2-fenilindol (MW: 350, DAPI²⁺), ethidium (MW: 394, Etd⁺) bromide, propidium iodide (MW: 668, PI²⁺), indocyanine green (MW: 774.96, ICG⁺) or Evans blue (MW: 961, EB⁻⁴) was monitored in time-lapse experiments. Pax1 hemichannels were neither activated by extracellular divalent cations-free solution nor inhibited by La³⁺. However, they were activated by stretch and inhibited by carbenoxolone (5 μ M). The uptake was transient and competitive and showed a Michaelis-Menten behavior with characteristic Km for each dye. HeLa-Pax1 cells did not present PI²⁺ uptake and uptake of all dyes was absent in HeLa-P cells. Therefore, the permeability of Pax1 hemichannels is poor for cationic molecules and much higher for anionic molecules

MECHANISM OF DEAFNESS MUTATIONS ASSOCIATED TO THE FIRST EXTRACELLULAR LOOP OF CX26 UNVEILS A NEW INTERACTION PROPERTY BETWEEN CONNEXINS.

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Mutations in Cx26 gene lead to genetic deafness, which can be nonsyndromic or syndromic, if deafness is associated to skin disease. Syndromic mutations located in the first extracellular loop of Cx26, like Cx26G59A, which cause palmoplantar keratoderma and deafness, are dominant. Interestingly, other mutation in this position (Cx26G59V) produces nonsyndromic deafness. Previous report shows that co-expression of Cx26G59A with wild-type (wt) Cx26 or Cx43 cause a decrease of function of Cx43. Because at normal conditions, Cx26 doesn't oligomerize with Cx43, the mechanism of negative dominance of this mutant over Cx43 function is intriguing. When expressed in HeLa Cells both mutants localized at cellular appositional membranes forming few and small GJ plaques compared to wtCx26. Consistently, cells that express the mutants have reduced intercellular coupling. Through velocity sedimentation analyses we found that that these mutations affected Cx26 oligomerization. Accordingly, biotinylation experiments indicated that these mutants doesn't reach plasma membrane. However co-expression of mutants with Cx43 allows mutant Cx26 to localize in large gap junction plaques, but mutants and Cx43 segregates in different areas of a gap junction plaque. Moreover, we found more mutant Cx26 in the plasma membrane but, co-expression of Cx43 with either mutant reduced coupling index. Our results suggest that there's another kind of interaction between Cx43 and these mutants that isn't typically hetero-oligomerization.

PRENATAL STRESS PRODUCES PERSISTENCE OF REMOTE MEMORY AND DISRUPTS FUNCTIONAL CONNECTIVITY IN THE HIPPOCAMPAL-PREFRONTAL CORTEX AXIS

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Prenatal stress is a risk factor for the development of neuropsychiatric disorders, many of which are commonly characterized by an increased persistence of aversive remote memory. Here, we addressed the effect of prenatal stress on both memory consolidation and functional connectivity in the hippocampal-prefrontal cortex axis, a dynamical interplay that is critical for mnemonic processing. Pregnant mice of the C57BL6 strain were subjected to restraint stress during the last week of pregnancy, and male offspring were behaviorally tested at adulthood for recent and remote spatial memory performance in the Barnes Maze test under an aversive context. Prenatal stress did not affect the acquisition or recall of recent memory. In contrast, it produced the persistence of remote spatial memory. Memory persistence was not associated with alterations in major network rhythms, such as hippocampal sharp-wave ripples or neocortical spindles. Instead, it was associated with a large decrease in the basal discharge activity of identified principal neurons in the medial prefrontal cortex as measured in urethane anesthetized mice. Furthermore, functional connectivity was disrupted, as the temporal coupling between neuronal discharge in the medial prefrontal cortex and hippocampal sharp-wave ripples was decreased by prenatal stress. These results could be relevant to understand the biological basis of the persistence of aversive remote memories in stress-related disorders.

ROLE OF CHLORIDE CO TRANSPORTERS IN AN ANIMAL SCHIZOPHRENIA MODEL

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Schizophrenia is psychiatric disease that affects ~1% of the worldwide population. Whose main characteristics are an altered perception of the reality and a disruption of formal thought. The principal symptoms of schizophrenia are listed in three large groups: Positives, Negatives and Cognitives. Besides the classical view that Dopamine system is alters, the GABAergic system is also involved in the development of Schizophrenia. The chloride co-transporters NKCC1 and KCC2, which maintain the intracellular chloride level, show an alteration in their expression ratio in cortex and hippocampus. In this study, we use Ketamine administration and maternal Deprivation to generate two Schizophrenia models to study the role of these transporters in the hippocampal formation. Schizophrenic-like animals showed a significant higher locomotor activity, exploratory behavior and time in movement, than in control animals. Synaptically evoked glutamatergic extracellular field potentials of the CA3-CA1, show a shift to the right in the input – Output curve, indicating a decrease in the system excitability. We found no significant changes in GABAergic responses after blocking NKCC1 with Bumetanide. However, in Dentate Gyrus, the gatekeeper of the hippocampus circuit, we found a decrease in the GABAergic system excitability after the treatment with Bumetanide in schizophrenia-like animals. In summary, we found both behaviorally and electrophysiological changes, which correlate with the function of NKCC1 activity in Dentate Gyrus of schizophrenia-like animals, suggesting a role of chloride balance in this psychiatric condition. **Funded by FONDECYT 1130904, CONICYT Anillo ACT-1113, INNOVACORFO 12IDL1-16078.**

LACK OF PANNEXIN 1 IN THE MURINE COCHLEA RESULTS IN SENSORINEURAL HEARING LOSS

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Pannexines (Panx) is one of the two protein families mediating the intercellular communication in vertebrates. Although expressed in the cochlea, whether these proteins play any role in hearing needs to be determined. Since Panx1 is expressed by the same cochlear cellular groups connected by connexine-based intercellular channels, we hypothesize that lack of Panx1 in the cochlea results in sensorineural hearing loss (SNHL). We addressed this question by assessing the hearing status of knockout mice for Panx1 (Pan1-KO). Click-generated auditory brainstem responses (ABR) were acquired in anesthetized 1 year old Pan1-KO mice (N=5) and the corresponding age-matched control (wild type) animals (N=7). In addition, histopathology of the different cochlear turns was analyzed by light microscopy. Although ABR were reliably obtained in Panx1-KO mice, hearing sensitivity was significantly decreased with regard to that observed in wild type individuals –i.e. mean electrophysiological thresholds exceeded the normal values in more than 20 dB. ABR of Panx1-KO individuals typically had lower amplitudes and longer latencies than control animals. SNHL was accompanied by an evident degeneration of the spiral ganglion in the basal turn of the cochlea, suggesting that most of the hearing impairment occurs at the high frequency region of the audible spectrum of the specie. We conclude that the lack of the Panx1 gene produce mild to severe deafness. Further studies are now needed in order to clarify the physiological mechanisms affected when the cochlear expression of this protein is missing.

NKCC1 INHIBITION DECREASE ALTERED EXCITABILITY OF DENTATE GYRUS IN ADULT EPILEPTIC CONDITIONS

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Granule cells of the dentate gyrus (GCDG) are the gatekeepers of hippocampal circuit by an intrinsically low cell excitability, which is pathologically increased in Temporal Lobe Epilepsy. Alterations in balance between excitation and inhibition in the nervous system are involved in several neurological conditions. γ -amino butyric acid (GABA) is the most important inhibitory neurotransmitter in the nervous system, however excitatory effects produced by this neurotransmitter have been observed in GCDG in epileptic patients. In this work, we wanted to study how intracellular chloride levels driven by $\text{Na}^+ \text{K}^+ \text{Cl}^-$ co-Transporter 1 (NKCC1) expression alter the circuit excitability in mature GCDG. Here, we show by extracellular field recordings of hippocampal slices the glutamatergic and GABAergic response, this by perforant path stimulation and granular stimulation respectively. Application of NKCC1 inhibitor –Bumetanide– produces a ~50% decrease in circuit excitability in synaptic and population spike signals of epileptic animals. Furthermore, the GABAergic responses also decrease ~40%. However, only 10% decrease in glutamatergic and GABAergic response was observed in control slices. These results suggest that NKCC1 has a low expression in mature tissue, but its expression increases in epileptic tissues, being responsible of the increase in excitability. This work is highly relevant because suggest a new pharmacological target for patients who do not respond to conventional treatments. FONDECYT 1130904, INNOVA-CORFO 12IDL1-16051.

ESTIMATING THE NUMBER OF INHIBITORY POSTSYNAPTIC DENSITIES OF SINGLE DOPAMINERGIC NEURONS OF THE MOUSE VENTRAL TEGMENTAL AREA (VTA)

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Midbrain dopaminergic neurons of the ventral tegmental area (VTA) are involved in several neural functions such motor control, behavioral reinforcement and motivation. The activity of VTA dopaminergic neurons is controlled by intrinsic membrane properties, as well as innervation from glutamatergic, cholinergic and GABAergic afferents, which form synapses within the somato-dendritic compartment. The present study aims to quantify the total number of GABAergic synapses onto individual dopaminergic neurons of the VTA, using a combination of electrophysiology, immunohistochemistry, confocal microscopy and stereology. In anesthetized mice, we recorded and labeled VTA single neurons using the juxtacellular technique. Later, neurobiotin-labeled neurons were identified as dopaminergic by their immuno-positivity for tyrosine hydroxylase (TH). Using double immunostaining for neurobiotin and the scaffolding protein Gephyrin (GEPH, a marker for inhibitory post-synaptic densities), inhibitory synaptic contacts were identified. Furthermore, confocal acquisition and 3D analysis of labelled structures allowed us to estimate the total number of GEPH profiles on the somata and dendrites of single TH+ VTA neurons. Preliminary results indicate that an individual VTA dopaminergic neuron in the mouse receives more than seven hundred inhibitory synapses.

PANNEXIN-1 CHANNEL BLOCKADE ABOLISHES THE ASTROGLIAL HYPEREXCITABILITY OBSERVED IN A RAT MODEL OF CHRONIC EPILEPSY.

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Currently, it is widely accepted that astrocytes plays an active role in several neuropathologies. In spite of that, how the astroglial function changes in pathological conditions remains unclear. Previously, we showed that hippocampal astrocytes from a kindled epileptic brain exhibit an augmented incidence of spontaneous ATP-dependent slow Ca^{2+} transients, which upregulates glutamate Ca^{2+} -dependent gliotransmission and therefore the strength of excitatory CA3-CA1 synapses. Because ATP is the main gliotransmitter involved in astrocyte-to-astrocyte communication, we assessed if this plays a role in this astroglial Ca^{2+} -mediated hyperexcitability. Astroglial Ca^{2+} imaging were carried out while blocking P2Y1 receptors (P2Y1R) and pannexin-1 formed hemichannels (PX1-HC) – one of the candidates for non-vesicular ATP-release – in control and kindled hippocampal slices. P2Y1R blockade reduces de the number of astroglial Ca^{2+} transients per area in control and kindled rats, with changing neither the duration nor the frequency in both control and kindled groups. However, the blockade of PX1-HC has no effect over astroglial Ca^{2+} transients in control slices, while in kindled ones diminishes the duration of Ca^{2+} signals, without affecting the frequency or the number of Ca^{2+} signals per area. These evidences suggest that astrocyte-astrocyte signaling via P2Y1R and PX1-HC plays a role in epilepsy physiopathology, likely contributing to the reduction of seizure threshold and epilepsy chronicity. Funding: 1130491 (CB) and 1130614 (MF) from FONDECYT, CID 1/2006 from DIPUV (CNPC), UVA 0804 2010 (JM) and UVA 0603 MECESUP fellows (CAF) and CONICYT 22120213 fellows (MW).

CHLORIDE CO-TRANSPORTER NKCC1 AS A NEW PHARMACOLOGICAL TARGET FOR ADULT CHRONIC EPILEPSY

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Epilepsy is a chronic disease characterized by periodic and unpredictable occurrence of seizures, due to high neuronal activity, product of a dysregulation of excitatory and inhibitory activity. Studies in neurons from epileptic tissue, have shown a higher concentration of chloride, producing a depolarization (excitatory effects). On the other hand studies in hippocampal slices, from animal models of acute epilepsy, have shown an over-expression of co-transporter NKCC1, which may be causing the increase in the chloride concentration. For neonatal it has been proposed that the specific blocker of NKCC1 Bumetanide can be used as antiepileptic. However it has not been evaluated if this is an useful treatment for adult chronic epilepsy. In the present study, in order to study the antiepileptic effect of Bumetanide, chronic epilepsy was induced in adult rats by pilocarpine administration. After 2 weeks, the epileptic animals were treated with the antiepileptic Diazepam (GABA agonist), Bumetanide (Blocker NKCC1), and the combination of both. o Diazepam treated animals showed seizures during the two first hours post-injection, suggesting that activating GABAergic transmission has excitatory effects. NKCC1 expression assayed showed an increase in epileptic animals, suggesting that the excitatory GABA effects arise from a reversion of chloride driving force. By the present work it is shown that animal models of chronic epilepsy do not respond to treatment with Diazepam, due to increased expression of the co-transporter NKCC1, and Bumetanide could be an effective antiepileptic drug for refractory epilepsy.

HERPES SIMPLEX VIRUS TYPE 1 ALTERS FUNCTIONAL DISTRIBUTION OF AMPA RECEPTOR AND NEURONAL PLASTICITY-ASSOCIATED PROTEIN ARC DURING NEURONAL INFECTION

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Herpes simplex virus type 1 (HSV-1) is ubiquitous, neurotropic, and the most common pathogenic cause of sporadic acute encephalitis in humans. Herpes simplex encephalitis is associated with a high mortality rate and significant neurological, neuropsychological, and neurobehavioral sequelae, which afflict patients for life. HSV-1 infects limbic system structures in the central nervous system, and has been suggested as an environmental risk factor for Alzheimer's disease. The activity-regulated cytoskeleton-associated protein (Arc) is a postsynaptic immediate early expression protein that has emerged as a key regulator of synaptic plasticity and memory consolidation. Regarding this, Arc regulates actin cytoskeleton rearrangements and AMPA receptors endocytosis to modulate these neuronal processes. Although, the role of Arc in neurogenesis and AMPA trafficking is clear, no studies have analyzed the effects of persistent neurotropic virus on Arc dysregulation and neuronal morphological and functional alteration. The present study evaluated the expression and subcellular distribution of Arc and AMPA receptor during neuronal HSV-1 infection using immunofluorescence analysis and western blot. Our results show an increase in the Arc protein evidencing a cytoplasmic localization at early times postinfection and perinuclear distribution at later times compared with mock-infected neurons. Also, an increase of GluR1 at the membrane level was observed during neuronal infection. Additionally, actin cytoskeleton rearrangements, as filopodia were observed during neuronal infection. These results suggest that alteration in Arc dynamic during HSV-1 neuronal infection modulates AMPA receptor distribution and modifies the actin-rich plasma-membrane protrusions. HSV-1 induced Arc and AMPA receptor dysfunction could have consequences in synaptic homeostasis, as well as implications in viral spread.

A BIOLOGICAL CONTEXT FOR THETA-FREQUENCY NEURONAL RESONANCE: A COMPARATIVE STUDY BETWEEN CORTICAL AMYGDALA AND HIPPOCAMPAL NEURONS

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Neurons from different memory-related mammalian brain regions display intrinsic maximal subthreshold voltage responses to oscillatory stimulation at theta frequencies (4-8 Hz; theta resonance). This may contribute to tune and stabilize network oscillatory activity. However, the drop in input resistance (R_{in}) produced by synaptic bombardment in active networks predicts a loss of resonance impact on neuronal processing. To investigate whether resonance drives rhythmic spiking in active networks we performed a comparative study of two resonant neuron populations with different R_{in} , CA1-pyramidal (~60 M Ω , CA1P) and cortical amygdala neurons (~160 M Ω , ACoN) using rat brain slices, whole-cell recordings, dynamic clamp and computational modeling. A hyperpolarization-activated cationic current (I_H) contributed to subthreshold resonance in both neuronal groups. Favored by the high R_{in} , I_H also filtered perithreshold voltage oscillations in ACoN, thus allowing the translation of resonance to spiking regimes even under recreated synaptic bombardment. In turn, CA1P displayed a tunable mechanism for resonance translation to spiking based on relative levels of a muscarine-sensitive potassium current (I_M) and a persistent sodium current (I_{NaP}). Notably, we confirmed the prediction of RLC-filter theory that changes in R_{in} due to synaptic bombardment modulate resonance frequency and strength. CA1P have five-fold more I_{NaP} than ACoN, increasing perithreshold impedance and thus compensating the low R_{in} . Therefore, neurons with opposed R_{in} values implement different strategies to effectively translate their frequency preference to spiking regimes. We present a novel aspect of neuronal resonance, consisting of a dynamic tunable mechanism for intrinsic frequency preference that depends on the level of network activity.

A DEVELOPMENTAL STUDY OF THE NEUROCHEMICAL IDENTITY AND AXONAL ENDINGS OF THE NUCLEUS ISTHMI PARS PARVOCELLULARIS IN *Gallus gallus*

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The isthmotectal circuit of the avian midbrain is composed by the nucleus isthmi pars parvocellularis (Ipc), pars semilunaris (SLu) and pars magnocellularis (Imc), all of them reciprocally connected to the optic tectum. The Ipc nucleus has been considered cholinergic because of its immunoreactivity for choline acetyl transferase (ChAT). However, recent results called into question the cholinergic phenotype of the Ipc, since its neurons express the mRNA for the vesicular transporter of glutamate (VGLUT2) and not for the vesicular transporter of acetylcholine (VACHT). To explore a possible change of the neurochemical phenotype of Ipc during development, we analyzed the expression of m-RNAs coding for three cholinergic proteins (ChAT, VACHT and the choline transporter, CHT) and for two glutamatergic ones (VGLUT2 and VGLUT3). We found that during E12-E16, the Ipc neurons showed a strong expression of m-RNAs for all cholinergic markers, and also for VGLUT2. After this period and through the postnatal stages, the expression of VACHT-mRNA became undetectable, whereas that of VGLUT2 mRNA remained unchanged. These results suggest that during E12-E16, the Ipc cells would be able to release acetylcholine and glutamate, and after that period, these cells would become predominantly glutamatergic. Since the neurotransmitter release has been involved in both dendritic and axonal growth, we decided to study the Ipc axonal development using neuronal tracers. While at E13 we could identify axons lacking of terminal branches, at E15 the neurons showed a dense and abnormally wide axonal arborization. From E18 onwards it was possible to identify mature axon-terminal endings. The development and maturation of the Ipc endings take place during the same period at which they might be releasing acetylcholine, suggesting a role for the cholinergic transmission on the development of the Ipc terminals.

METHYLPHENIDATE (MPH) INCREASES THE LTP BY PHOSPHORYLATION OF SERINE 845 OF GLUR1 SUBUNIT OF AMPA RECEPTOR IN HIPPOCAMPUS.

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Methylphenidate (MPH, Ritalin©) is widely used in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and recently as abuse drug. It is known that MPH increases extracellular levels of dopamine and noradrenaline by blocking monoaminergic transporters. Recently, our group and others have shown that acute applications of MPH, increase, in a dose-dependent manner, the TBS-dependent LTP in CA3-CA1 synapse of rat hippocampal slices. However, the molecular mechanisms involved in this process are still unknown. We hypothesize that the facilitation of TBS-dependent LTP induced by MPH involve the insertion of new AMPA receptors in the post-synaptic membrane induced by phosphorylation of Ser845 residue in the GluR1 subunits. Our experimental approach was to collect CA1 areas from hippocampal slices used in experiments of LTP, and the further analysis by Western blot of the phosphorylation state of Ser845 and Ser831 residues in GluR1. CA1 areas from slices that shown an enhanced TBS-dependent LTP after perfusion with 5 μ M MPH shown a significant increase of the 28 ± 6 % in the phosphorylation of Ser845 residue (n=6,6; * p<0.05) respect to control slices (TBS-dependent LTP without MPH). This modification was detected specifically on Ser845 residue and no significant change in the phosphorylation state of Ser831 was observed (n=6,6; p > 0.05). These results suggest that MPH increase the TBS-dependent LTP in CA3-CA1 synapses promoting the insertion of AMPA receptors in the postsynaptic membrane through phosphorylation of Ser845 residue in GluR1 subunits. **Supported by FONDECYT 1120580, Anillo ACT-1113 and CONICYT Fellowship to C.C./D.C.**

COORDINATION OF NEUROVASCULAR COUPLING VIA ATP RELEASE FROM ASTROCYTES IS CONTROLLED BY NO-DEPENDENT OPENING OF PANNEXIN-1 CHANNELS

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Neuronal activity depends on timely, close regulation of cerebral blood flow through the mechanism known as neurovascular coupling. Astrocytes are located in a strategic position to mediate and coordinate the communication between neurons and arterioles, in part, via ATP release. Astrocytes express the enzyme endothelial nitric oxide synthase (eNOS) and the gap junction protein connexin 43 (Cx43). In astrocytes, Cx43 can form gap junction channels or hemichannels, similar to those formed by pannexin-1. Nitric oxide (NO) may activate Cx43 hemichannels. Then, we evaluated if ATP release from astrocytes is mediated by NO-dependent activation of Cx43 hemichannels or pannexin-1 channels. We used primary astrocyte cultures to assess NO production and ATP release in response to glutamate or the agonist of glutamate metabotropic receptor, t-ACPD. Furthermore, hemichannels activation was evaluated by ethidium uptake and protein expression by immunofluorescence and Western blot. In addition to Cx43 and eNOS, the expression of pannexin-1 was also detected in astrocytes. Stimulation of astrocytes with glutamate or t-ACPD induced an increase in NO production, ethidium uptake and ATP release. The increase in ethidium uptake and ATP release was abolished by the blockade of NO production with 100 μ M N^G-nitro-L-arginine (L-NA). ATP release was also blocked by the pannexin-1 channel blocker ¹⁰panx, but only attenuated by the Cx43 channel blocker ^{37,43}Gap27. These results suggest that ATP release evoked by the stimulation of astrocyte glutamate metabotropic receptor in the neurovascular coupling depends on pannexin-1 channel opening through the activation of NO production.

Proyecto Puente 30/2014

THE NEURONAL ACTIVITY OF THE CEREBRAL GANGLION IN THE ANTARCTIC LIMPET *NACELLA CONCINNA* IS TUNED TO WORK AT LOW TEMPERATURE

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The Antarctic organisms have undergone a series of biological and neurobiological adaptations which allow living in extreme environments as Antarctica, characterized by low water temperature ($\sim -2^{\circ}\text{C}$). In the Antarctic Peninsula, one of the most prominent species of geographical distribution and dominance in the benthic zone is the Limpet *Nacella concinna*. In this work we study the temperature dependence of extracellular field potentials of the cerebral ganglion from *N. concinna* specimens that were collected from Fildes Bay ($62^{\circ} 12.0' - 58^{\circ} 57' 51''$), in Antarctic Peninsula. Field potentials were obtained by suction electrodes in right and left portions of cerebral ganglia by applying slow ramps of temperature. The range of temperature was from 0°C to 12°C . The signal obtained was filtered using a low-pass 4-pole Bessel filter and analyzed offline, in order to compare the electrical activity in different temperature windows. Also, comparison among different subjects was done using spike sorting and cluster analysis. We found that electrical activity of *N. concinna* shows the maximal firing frequency between $0-6^{\circ}\text{C}$, while in temperatures above 6°C the activity decreases dramatically. In comparison, spontaneous firing in cerebral ganglia of land snail *Helix aspersa*, a mollusk with a different thermal environment, shows a peak frequency around 15°C , and a decrease of frequency at both higher and lower temperatures. These results show that this invertebrate nervous system is adapted to fire action potentials in a temperature range in which template species cannot sustain repetitive firing. Funded by INACH RT_15-12, CONICYT Anillo ACT-1113.

NEW INSIGHTS ON AN ENDOGENOUS CAMKII INHIBITOR UPREGULATED AFTER LTP

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Both the activity of Ca²⁺/calmodulin-dependent kinase II (*CaMKII*) and its binding to the NMDA receptor (*NMDAR*) are essential for long-term potentiation (*LTP*), a form of synaptic plasticity implicated in learning. A specific inhibitor of this kinase, named **CaMKIIN**, is present in the same CaMKII-containing cells. Moreover, **CaMKIIN** interferes with kinase binding to the NMDAR. **CaMKIIN** expression is increased after learning, suggesting a role in plasticity regulation. However, **CaMKIIN** size and localization are controversial: while it was first described as a soluble 8kD protein, later studies suggested it to be larger and enriched at synapses. **CaMKIIN** characterization is required to elucidate a possible role in plasticity of this CaMKII regulator. We aimed to determine basal **CaMKIIN** subcellular localization and to evaluate if their levels or distribution are modified after chemically-induced LTP (cLTP) in rat cultured hippocampal slices. **CaMKIIN** was detected by western blot with an antibody validated by its capacity to detect a band from a homogenate of HEK cells overexpressing the described 8kD sequence. Interestingly, when tested on diverse brain samples where **CaMKIIN** should be present, the antibody detected a ~30kD band, while the 8kD band was absent. In slices, the 30kD band was present in membrane and cytosolic fractions, and our preliminary results show an increase in both fractions after cLTP. Therefore, **CaMKIIN** could be a larger protein than predicted, perhaps due to alternative splicing or oligomerizations. Moreover, **CaMKIIN** upregulation after cLTP further supports a role as plasticity-related protein that may regulate CaMKII activity and localization.

ANATOMICAL AND PHYSIOLOGICAL ORGANIZATION OF PARAVENTRICULAR NUCLEUS OF THALAMUS NEURONS

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We investigate the anatomical and physiological organization of the paraventricular nucleus (PVT), as well as its role in shaping patterned activity in the nucleus accumbens (NAc). In order to determine the anatomical and physiological organization of the PVT, we have been using the juxtacellular method, so we can achieve single-neuron resolution. So far, we have recorded and labelled forty-four PVT neurons, with characterized neurochemical profiles and firing patterns. Based on the expression patterns of two calcium-binding proteins, calbindin and calretinin, we describe four different anatomical profiles. However, physiological parameters, including discharge rate, spike waveform, and spike timing, do not support the existence of distinct cell types in the PVT. Therefore, neurochemical diversity of PVT neurons has no apparent physiological correlate. Finally, we determine the role of the PVT in shaping patterned activity in the NAc, we have performed simultaneous recordings in single PVT neurons and local field potentials in the NAc. Previous studies have demonstrated that the NAc exhibits prominent gamma activity, which we detect in our preparation. However, our results suggest that individual PVT neurons do not contribute to gamma activity in NAc. So far, our results indicate that similar types of neurons compose PVT, even though these neurons express different neurochemical profile, the physiological patterns also indicate that PVT neurons are similar. On the other hand, the individual PVT neurons are not capable to contribute to gamma activity in NAc.

USING STEREOLOGICAL TOOLS TO STUDY SOMATIC, NUCLEAR AND DENDRITIC COMPARTMENTS OF NIGRAL DOPAMINERGIC NEURONS IN THE MOUSE

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Dopaminergic neurons of the substantia nigra are relevant for motor control and motivated behavior. Dysfunction of these neurons is responsible for various neurological and psychiatric diseases, as well as addiction. Previous studies have shown that dendritic structure in dopaminergic neurons relates to their pattern of activity. Evidence also shows that morphological changes in neuronal structure occur concomitantly with disease progression. Thus, in order to unveil the substrates underlying function and dysfunction of dopaminergic neurons, it is relevant to describe the structure of neurons in detail. We carried out a pilot study to determine the size and complexity of different subcellular structures using stereological probes in C57BL/6 mouse brain tissue stained for the enzyme tyrosine hydroxylase (TH). First, we applied the Cavalieri method to determine the total volume of TH+ cell bodies, the nuclei of those cell bodies, as well as the TH+ dendrites and axons contained in the neuropil. Preliminary results indicate that cell bodies, nuclei and neuropil occupy a volume of 20×10^6 , 4×10^6 and $31 \times 10^6 \mu\text{m}^3$ respectively. Second, we applied the optical fractionator to estimate the total number of bifurcations observed in the neuropil of the substantia nigra, mostly of which correspond to dendritic bifurcations. Also we estimated the number of cell bodies. Preliminary results indicate a mean of 23,724 bifurcations in the substantia nigra, with a total of 4 to 7 bifurcations per neuron. This data will complement our single neuron studies of dopaminergic neurons. In addition, we plan to apply these analyses to study early morphological changes preceding pathological states using models of Parkinson is disease.

ROLE OF CALCIUM AND cAMP SIGNALING IN THE PROTHORACIC GLAND IN THE CIRCADIAN TIMING OF *DROSOPHILA* EMERGENCE

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The circadian clock of *Drosophila* restricts the time of emergence of the adult fly to the early part of the day. The emergence of the adult fly is the culmination of the developmental process of metamorphosis, which is controlled by the steroid molting hormone, 20-hydroxy-ecdysone (20E). The prothoracic gland (PG) is a peripheral gland that produces ecdysone (the 20E precursor). The PG also contains a circadian pacemaker that, together with the central pacemaker in the brain, controls the timing of adult emergence. We investigated the role of cyclic AMP (cAMP) and calcium (Ca²⁺) in the functioning of the peripheral (PG) clock. Our results show that genetic manipulations that produce sustained changes to cAMP and Ca²⁺ levels in the PG cause, respectively, a shortening and a lengthening of the period of eclosion compared to that of controls. In addition, we used genetically encoded cAMP (epac) and Ca²⁺ (GCaMP) sensors to show cAMP and Ca²⁺ levels vary in the PG during the course of the day under both LD and DD conditions. These results indicate that levels of these second messengers can alter the functioning of the clock itself, suggesting that cAMP/Ca²⁺ could be part of a homeostatic mechanism through which physiological stimuli external to the circadian clock can alter its period. These results are relevant for understanding how clocks and an organism's physiological state are coordinated to produce a unified internal time.

CHRONIC EXPOSURE TO FLUOXETINE DURING PERINATAL PERIOD DIMINISHED SEROTONIN ACTIVATION OF FICTIVE RESPIRATION IN NEONATAL MICE

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Serotonin (5HT) is known to play a principal role during development of SNC in mice (Gaspar et al., 2003, *Nat. Rev. Neurosci.* 4: 1003). We have documented the reduced ventilatory response to hypercarbia in neonates exposed to fluoxetine (specific 5HT reuptake inhibitor) during pregnancy (Bravo et al., 8th FENS Forum Neuroscience 2012). Activation of raphe and tractus solitarius nuclei, determined by c-Fos expression, was decreased in fluoxetine treated animals compared with controls. Acidosis stimulated increase in frequency of fictive respiration was also diminished in fluoxetine exposed neonates (Bravo et al., PanAm, 2014). In the present work we investigated if fluoxetine treatment alters 5HT activation of fictive respiration.

Osmotic minipumps were implanted to CF-1 dams on day 5 of pregnancy to deliver fluoxetine (7mg Kg⁻¹ day⁻¹) for up to 28 days. Mice without minipumps were used as control. The frequency of fictive respiratory activity was recorded from ventral respiratory column (VRC) in brainstem slices from P8 neonates. 5HT was applied to the superfusion fluid.

In control animals, 5HT increased frequency of fictive respiration in a dose dependent manner. In fluoxetine treated neonates the effect of 5HT was almost abolished, Both the sensitivity and reactivity of the dose response curve was seriously diminished. Our results suggest that fluoxetine treatment during perinatal period alters the serotonergic drive of the respiratory network and the functional connection between raphe and VRC in neonates.

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