Sociedad Chilena de Neurociencia

XV ANNUAL MEETING OF THE CHILEAN SOCIETY FOR NEUROSCIENCE

Club La Serena, La Serena,
November 5-7, 2019

ABSTRACTS BOOK

socneurociencia.cl/congreso-2019/

XV Annual Meeting of the Chilean Society for Neuroscience

5 to 7 November 2019

La Serena, Chile.

Hotel Club La Serena

MESSAGE FROM THE PRESIDENT

Welcome to the XV Annual Meeting of the Sociedad Chilena de Neurociencia (SCN) in La Serena

Since our origins, one of the aims of the SCN has been to bring science to society. During the past weeks the Chilean Society is demanding for new ways in which our economical system is arranged. Socio-economical paradigms that have been pushed forward for decades have done nothing but to increase the inequality among us. In these very same days, the Chilean Science system is being re-formulated. Perhaps, it is time to incorporate in our scientific organizations and duties a stronger sense of community, being always attentive to the country's needs. Also, we have to re-think the way our scientific productivity is measured, ranked and rewarded, in order to avoid falling (again) in the trap of a selfish, monopolistic and utterly competitive funding scheme. Biology and Neuroscience are so eloquent in saying that the route to success is the promotion of variety and cooperation, that we should be the first ones to embrace those as first priorities to guide our activities.

Understanding how our brain works allow us to understand complex phenomenons in cognition, emotion, learning and other higher brain functions. For this annual meeting we have one Satellite and several Symposia organized specifically to understand brain functions, reflexing an increase in the interest in our local community for these aspects of neuroscience. For this annual meeting we have one satellite, eight symposiums, three plenary conferences, two oral communications and two poster session covering from molecular to cognitive aspects of neuroscience. One of these events is the Young Neuroscientist Symposium, an instance to potentiate the early career in science.

On behalf of the Directory of the SCN, I would like to welcome and invite you to enjoy the meeting.

Dr. Patricio Rojas
President
Sociedad Chilena de Neurociencia

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CONGRESS PROGRAM

Hora	November 5th	Hora	November 6th	Hora	November 7th
09:00 12:30	**REGISTRATION**	09:00 11:00	**SYMPOSIUM 3:** **The Dynamics of Brain States: Theory, Simulations and Behavior** Room: Elqui 1	09:00 11:00	**SYMPOSIUM 5:** **Neuroscience of bistable stimuli: a window to brain function"** Room: Elqui 1
09:00 12:00	**SATELLITE:** **Perspectives in Neuroscience** Room: Elqui 1	09:00 11:00	**SYMPOSIUM 4:** TRP channels in cell physiology and physiopathology Room: Elqui 2	09:00 11:00	**SYMPOSIUM 6:** **Small Brains in Neuroscience** Room: Elqui 2
		11:00 11:30	**COFFEE BREAK**	11:00 11:30	**COFFEE BREAK**
		11:30 12:00	**CONOCIENDO NUESTRO CEREBRO: UN ACERCAMIENTO A LA NEUROCIENCIA**	11:30 12:30	**PLENARY LECTURE 2** **Pathophysiology of cold-activated TRP channels** **Felix Viana** Room: Elqui 3
		12:00 12:30	**LATBRAIN INITIATIVE**		
12:30 14:30	**LUNCH BREAK**	12:30 14:30	**LUNCH BREAK**	12:30 14:30	**LUNCH BREAK**
14:30 16:30	**SYMPOSIUM 1:** **From local to large-scale human neurodynamics: new insights from fMRI and intracranial recordings** Room: Elqui 1	14:30 16:30	**ORAL COMUNICATION I** Room: Elqui 1	14:30 16:30	**SYMPOSIUM 7:** **Insights into cognitive coding in the auditory system** **Room: Elqui 1**
14:30 16:30	**SYMPOSIUM 2:** Brain mechanisms associated to memory and Psychiatric disorders Room: Elqui 2	14:30 16:30	**ORAL COMUNICATION II** Room: Elqui 2	14:30 16:30	**SYMPOSIUM 8:** The Design, Distribution, and Use of Open Source and Low Cost Tools for Science Room: Elqui 2
16:30 17:00	**COFFEE BREAK**	16:30 17:00	**COFFEE BREAK**	16:30 17:00	**COFFEE BREAK**
17:00 18:30	**WELCOME** **PLENARY LECTURE 1** **The neural circuits of emotion** **Andrew Holmes** Room: Elqui 3	17:00 19:00	**YOUNG SCIENTIST SYMPOSIUM** Room: Elqui 3	17:00 18:00	**ASAMBLEA SOCIOS** Room: Elqui 3
				18:00 19:00	**PLENARY LECTURE 3** **CONFERENCIA DR. MARIO LUXORO** **Juan Bacigalupo** Room: Elqui 3
19:00 20:00	**COCKTAIL**				
20:00 23:00	**POSTER SESSION I**	20:30 23:00	**POSTER SESION II**	20:30 03:00	**DINNER PARTY**

CONFERENCES

The neural circuits of emotion

Andrew Holmes[1].
(1) LBGN, NIAAA

Trauma-related and anxiety disorders are the most prevalent group of psychiatric diseases, and there is growing medical need to improve on the effectiveness and the side effect profile of existing anti-anxiety drugs. Many years of preclinical pharmacological research has generated a huge amount of data and has led to numerous clinical trials – but this has led to very few translational success stories. There is therefore an urgent need to find a more productive dialog between preclinical models and clinical studies that is powered by an ever-developing appreciation of the shared neural circuits and genetic architecture that moderate anxiety-related behaviors across species. Innovative approaches will be discussed, using recent exemplars from state-of-the-art neuroscience experimentation in animal models, which have the potential to deliver a new generation of risk biomarkers and therapeutic strategies for trauma and anxiety disorders.

For more info: http://niaaa.nih.gov/research/niaaa-intramural-program/niaaa-laboratories/laboratory-behavioral-and-genomic-neuroscience

Pathophysiology of cold-activated TRP channels

Felix Viana[1].
(1) Instituto de Neurociencias de Alicante, Universidad Miguel Hernández-CSIC, San Juan de Alicante , ES

Sensing temperature is fundamental in the physiology of all organisms. It is important in food and habitat selection, and for the avoidance of noxious stimuli. In homoeothermic animals (mammals and birds), temperature sensing is also critical for thermoregulation. TRP Melastatin 8 (TRPM8), a polymodal, non-selective cation channel activated by cold temperature and chemical cooling agents (e.g. menthol), expressed in a fraction of primary sensory neurons, is widely accepted as the principal molecular sensor of mild cold temperatures. The contribution of TRPM8 and other TRP channels to noxious cold sensing is still a matter of debate. In this lecture, I will try to summarize efforts from our research group during the past two decades in dissecting the role of TRPM8 and other ion channels in cold temperature detection and thermoregulation. In this journey, we will make brief stops in some of the places and questions that have caught our attention. I hope to synthesize our current view of the molecular and cellular characterization of cold-sensitive neurons in mammals and a definition of their molecular diversity, combining transcriptional profiling and functional characterization. I will show how other ion channels shape the activity of cold thermoreceptors, the post-translational regulation of TRPM8 function and the identification of novel regulators of TRPM8 channels that provide novel perspectives on TRPM8 gating. Another important question is the mechanism(s) underlying cold hypersensitivity following nerve damage. Recently, combining in-situ hybridization and transgenic reported mouse lines, we described the expression of TRPM8 channels in different tissues and selective regions of the brain involved in thermoregulation. These results, combined with our characterization of metabolic disturbances in TRPM8 KO mice, provides some novel insight about the multiple roles of this fascinating channel in animal physiology.
Funded by project SAF2016-77233-R and co-financed by the European Regional Development Fund (ERDF) and the “Severo Ochoa” Programme for Centres of Excellence in R&D (ref. SEV- 2013-0317).

SYMPOSIUM

NEUROSCIENCE CENTERS SATELLITE SYMPOSIUM

Perspectives in Neuroscience: Ecological approximation to brain cognition

Chair: Pedro Maldonado

Using intracranial EEG to understand neuronal mechanisms in ecological environments: pros and cons

Jean-Philippe Lachaux. CNRS, laboratoire Dynamique cérébrale et cognition (Inserm)à Lyon.

Perceptual bistability as inference

Rubén Moreno-Bote.Center for Brain and Cognition , Universidad Pompeu-Frabra, Barcelona, Spain

Heart-brain interactions in emotion and memory

Sarah Garfinkel, UniversIty of Sussex

Non-ordinary states of consciousness in context

Enzo Tagliazzuchi. Universidad de Buenos Aires, Argentina

SYMPOSIUM

From local to large-scale human neurodynamics: new insights from fMRI and intracranial recordings

Chair: Tomas Ossandon

Transition graphs of human functional brain networks reveal complex, cost-efficient and behaviorally-relevant temporal paths

Juan Pablo Ramirez-Mahaluf[2], Vicente Medel[2], Joao Sato[1], Tomás Ossandón[2], **Nicolas Andres Crossley[2]**.
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(2) Psiquiatria, Medicina, Pontificia Universidad Catolica De Chile

Resting-state functional MRI activity is organized as a complex network; however, this coordinated brain activity changes with time. There is a need to develop paradigms that would allow us to understand this evolving activity. We explored the temporal organization of resting-state brain networks from 160 subjects from the Human Connectome Project, by looking at transition graphs of network activity. Nodes of these graphs corresponded to whole-brain connectivity patterns (or meta-states), and directed links the temporal transition between consecutive meta-states. We found that transition networks had several non-trivial properties, such as a heavy-tailed degree distribution and modular organization. This organization was implemented at a low biological cost with a high cost-efficiency of the dynamics. Global efficiency, local efficiency and transition cost of these networks were associated with cognition and motor functioning. We conclude that the temporal organization of brain activity has a complex organization and is related to behavior.

This work was funded by CONICYT PIA ACT 1414, CONICYT FONDECYT postdoctorado (Ref: 3190311 to JPRM), CONICYT FONDECYT regular (Ref: 1160736 to NAC), andCONICYT FONDECYT regular (*Ref:*1180932 to TO).

Human anterior insula encodes prediction error through amplitude modulation of beta oscillations

Tomas Ossandon[1,2], Pablo Fuentealba[2], Jean-Philippe Lachaux[3], Pablo Billeke[4].
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(2) Pontificia Universidad Católica de Chile, CL
(3) INSERM, CRNL, FR
(4) Universidad del Desarrollo, CL

Adaptive behaviour requires the comparison of outcome predictions with actual outcomes. This comparison is evaluated in terms of prediction error, which is computed by a distributed brain network comprising the medial prefrontal cortex (mPFC) and the anterior insular cortex (AIC). These areas are the main cortical target of mesolimbic dopaminergic neurons signalling prediction error during reinforcement learning. Despite being consistently co-activated during performance monitoring, the precise neuronal computations in each region and their interactions remain elusive. In order to assess the neural mechanism by which AIC processes performance feedback, we recorded AIC electrophysiological activity from 21 neurosurgical epileptic patients with intracerebral deep electrodes for presurgical evaluation while they carried out various cognitive tasks with continuous performance feedback. We tested the hypothesis that the AIC encodes performance feedback to adapt ongoing behaviour to environmental conditions. In particular, we predicted that the electrophysiological activity of the AIC is modulated by prediction errors, and that it exerts a causal influence on other cortical areas related to feedback processing and reward-based learning, such as the medial prefrontal region. We found that the AIC encodes unsigned prediction error through specific amplitude modulation of beta oscillations. Furthermore, the valence of feedback was encoded by delta waves phase-modulating the power of beta oscillations. Finally, connectivity and causal analysis showed that beta oscillations relay prediction error signals to mPFC. These results reveal that structured oscillatory activity in the anterior Insula encodes prediction error and performance feedback valence, thus coordinating brain circuits related to reward-based learning
Fondecyt 1180932, Anillo ACT1414

Multilevel brain connectivity during NREM sleep: an insight from intracranial electrodes

Mario Valderrama[1].
(1) Ingeniería Biomédica, Ingeniería, Universidad de Los Andes

Sleep is highly necessary for several functional and cognitive processes. Specifically, it is thought that during non-REM (NREM) sleep an active memory consolidation process takes place, where recently acquired information is distributed between different brain areas for its long-term storage. In order to study the dynamic interaction among these regions, different studies have reported the evolution of brain connectivity over different sleep stages leading to the identification of functional most connected areas. However, most of these analyzes have been based on fMRI or scalp EEG techniques that do not allow the mapping of brain activity at specific intracerebral locations with high temporal resolution. In consequence, we studied the brain connectivity during NREM sleep through complex networks constructed from intracranial electrodes. From these graphs, we identified several highly connected areas associated with slow oscillations (0.3–4 Hz), spindles (8-18Hz) and gamma (30-100Hz) rhythms, which are known to play an important role in different cognitive processes during sleep.

Intracortical EEG Amplitude-amplitude correlation in the high frequency band: a possible signature of transient cortico-cortical functional interactions”

Lachaux J [1]
(1) INSERM.CNRS

Human intracranial EEG (iEEG) recordings are primarily performed in epileptic patients for presurgical mapping. When patients perform cognitive tasks, iEEG signals reveal high-frequency neural activities (HFAs, between around 40 Hz and 150 Hz) with exquisite anatomical, functional and temporal specificity. Such HFAs were originally interpreted in the context of perceptual or motor binding, in line with animal studies on gamma-band (‘40 Hz’) neural synchronization. Today, our understanding of HFA has evolved into a more general index of cortical processing: task-induced HFA reveals, with excellent spatial and time resolution, the participation of local neural ensembles in the task-at-hand, and perhaps the neural communication mechanisms allowing them to do so.

Brain mechanisms associated to memory and Psychiatric disorders

Chair: Jimmy Stehberg

Impact of Stress and Diet on Neuropsychiatric Disorders

Alexies Dagnino[1].
(1) Laboratory of Stress Neurobiology, Center for Neurobiology and Integrative Pathophysiology, Institute of Physiology, Faculty of Sciences, Universidad de Valparaíso, Valparaíso, CL

In modern lifestyle, stress and Western diets are two major environmental risk factors involved in the etiology of neuropsychiatric disorders. Lifelong interactions between stress, Western diets, and how they can affect brain physiology, remain unknown. Pharmacological experiments and *in vivo* electrophysiological recording in behaving rats were performed to explore the effects of stress and diet on episodic and emotional memories. We demonstrated that the cannabinoid receptor type 1 (CB1) modulates the effects of chronic distress and dietary long chain polyunsaturated fatty acids (PUFAs) on memory retrieval in stressed rats. Our results suggest that endocannabinoid system is highly active in stressed animals supplemented with n-6 PUFA, since their memory improved when treated only with AM251 (CB1 antagonist), compared to those that were treated with a vehicle. In conclusion, this study proposes that endocannabinoids and PUFAs can both become a singular system by being self-regulated in limbic areas, so they modulate the effects of stress on the brain throughout a lifetime. Alterations at this level could increase vulnerability to neuropsychiatric disorders in human beings.

FONDECYT Regular (Grant Number 1141276) and Anillo de Ciencia y Tecnología, Programa PIA of CONICYT (Grant Number ACT1403) to Alexies Dagnino-Subiabre.

Role of the Nicotinic Acetylcholine Receptors Mediating the Enhancement of contextual fear extinction induced by Cotinine?

Echeverria Valentina M [1,2], Alexandre Iarkov[1], Florencia Echeverria[1], Nelson Perez-Urrutia[1], Patricia Oliveros-matus[1], Nathalie Alvarez-Ricartes[1].
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(2) Research & Development, Bay Pines VAHCS FL USA, Bay Pines, US

Cotinine is an allosteric modulator of the a7 and a4b2 nicotinic acetylcholine receptors (nAChRs). We have recently reported that cotinine alone or in combination with krill oil facilitated fear memory extinction and diminished depressive-like behavior at a dose ten times lower than the previously effective oral treatment in mice. In here, we study the effect of cotinine infused directly into the mPFC on locomotor activity, anxiety, depressive-like behavior, and fear extinction (FE). Also, to assess the role of a7- and a4b2nAChRs in the medial prefrontal cortex (mPFC) on cotinine´s effects, mice were infused with cotinine alone or in combination with the nicotinic receptor antagonists, methyllycaconitine (MLA, a7), or dihydro-beta-erythroidine (DHbE, a4b2). The infusions were carried out using ALZET osmotic mini-pumps installed under the skin of the back. Three days after the pump implantation, mice were subjected to fear conditioning (FC) followed by a week of extinction trials. Then mice were tested for locomotor activity (open field test), anxiety (light/dark box test), and depressive-like behavior (forced swim test). Next day, mice were euthanized, and the mPFC was analyzed for changes in GFAP+ astroglia cells by immunohistochemistry. The results show that FC reduced the number of astrocytes and their structural complexity. Cotinine infused in the mPFC improved fear extinction, reduced depressive-like behavior and prevented astrocytes deficit after FC. Interestingly, DHbE inhibited the cotinine-induced astrocytes resilience and antidepressant effects. The enhancement of fear extinction by cotinine was dependent on the a7nAChR and also influenced by a4b2 receptors as it was counteracted by MLA, and enhanced by DHbE co-infusion in the mPFC. The results strongly suggest that nAChRs are involved in cotinine´s actions on contextual fear extinction.

Fondecyt regular 1190264

Activation of the eEF2 pathway in the dentate gyrus excitatory neurons enhances cognitive function and neurogenesis in young and old mice

Yaacov Rozenblum[1].
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Background: Regulation of mRNA translation to protein plays a pivotal role in learning and memory formation. Protein synthesis is a dynamic process, which is regulated at three mainphases: initiation, elongation, and termination. While the initiation phase of translation is considered to be the rate-limiting step, regulation of the elongation phase via eukaryotic elongation factor 2 kinase (eEF2K) has also been suggested to be important for memory and synaptic plasticity consolidation (Taha E et al., 2013, 2016). During the elongation phase, eukaryotic elongation factor 2 (eEF2) promotes ribosomal translocation that leads to ribosomal movement along the mRNA. Phosphorylation of eEF2 on Thr56 by its specific kinase, eEF2K, inactivates eEF2 and leads to protein synthesis inhibition. Here, we aim at examining the function of the eEF2 pathway in the dentate gyrus (DG) of the hippocampus in mice.

Results: Proteomic analysis of hippocampus from mice with genetic deletion of eEF2K (knockout, KO), which leads to complete loss of eEF2 phosphorylation, revealed enriched fraction of proteins that are crucial for neurogenesis. Indeed, both neurogenesis and dentate gyrusdependent context discrimination learning were enhanced in the eEF2K KO mice compare to wt.

Using injection of viruses harboring Cre recombinase under the neuron-specific synapsin or excitatory neuron-specific CaMKII promoters into the DG of eEF2K floxed mice, we measured enhanced neurogenesis. In addition, LTP recordings performed in the dentate gyrus of CaMKII cre and GFP injected mice showed higher excitability levels in CaMKII cre mice compared to controls. Importantly, enhanced neurogenesis and context discrimination can be achieved also in aged CaMKII cre injected mice.

Conclusions: Together, our findings reveal that the eEF2K pathway in granular DG excitatory neurons plays a specific and critical role in neurogenesis and DG-dependent behavior. In addition, rejuvenation of the DG by modulating eEF2 phosphorylation in adulthood and aging enhanced memory precision. Our study suggest that eEF2K inhibition has potential therapeutic significance

in cognitive declined associated with aging.

Astroglial regulation of glutamatergic transmission via release of glutamate and D-serine is necessary for short-term fear memory and their excessive release during chronic stress contributes to the development of depression

Jimmy Stehberg[1].
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Astrocytes have been the focus of much attention recently, as they participate at synapses by releasing neuroactive molecules (dubbed gliotransmitters), including glutamate, GABA, ATP, and NMDAR co-agonists glycine and D-serine. Connexin 43 hemichannels (Cx43 HCs) are among the gliotransmitter release mechanisms found in astrocytes but not in neurons. We have found that Cx43 HCs mediate the astroglial release of D-serine and glutamate during fear memory training in the basolateral amygdala, regulating NMDAR activity and allowing the formation of short-term memory and later memory consolidation, but are not involved in learning per se. After Chronic stress, Cx43 HCs increase their activity, leading to a massive release of glutamate, ATP and possibly D-serine, contributing to the development of depressive symptoms, possibly by increasing NMDAR activity and increasing presynaptic release of glutamate in depression-relevant areas such as the hippocampus. Here we discuss the evidence so far and propose a novel model for the astroglial regulation of glutamatergic transmission necessary for memory and how its overactivation during chronic stress contributes to the development of depression.

FONDECYT 1160986

The Dynamics of Brain States: Theory, Simulations and Behavior

Chair: Patricio Orio

Dynamic Brain-state allocation in heath and neurodegeneration

Wael El-Deredy[1], Nelson Trujillo-Barreto[2], David Araya[3], Aland Astudillo[3].
(1) Ingenieria Biomedica, Ingenieria, Universidad de Valparaiso
(2) Neuroscience and Experimental Psychology, University of Manchester, Manchester, GB (3) Universidad de Valparaíso, CL

At the moment, when a patient presents with clinical symptoms of Parkinson's or Alzheimers disease there is very little the clinical community can do other than to manage the symptoms of what are inevitably degenerative conditions. Alterations in the neural state (or states) that eventually will produce functional and behavioural consequences had been set in motion perhaps 20 years earlier, and provoked the search for proper biomarkers in asymptomatic individuals. The reorganisation of functional brain networks, either due to slow changes in the relative contribution/ wiring of brain areas (plasticity) or due to fast modulation of their causal interactions (effective connectivity), mask the early stages of neurodegeneration, until alterations cannot be compensated. Until recently, approaches to brain function in health and disease mostly did not take in account of the fact that the brain highly dynamic, and that studying brain function as a series of static states may not be the most effective way to encountering early biomarkers for neurodegeneration. Rather, the clues might lay in the path or trajectory by which functional brain networks evolve and transition over time or their dwell time irregularities. Methodologically, estimating the evolution of the non-stationary and non-linear brain is challenging. Most solutions apply a fixed predetermined moving window, over which functional connectivity is estimated, thus missing the explicit modelling of the dynamical regimes, across multiple temporal length-scales, over which the brain networks are assumed to switch, from few multi-seconds to seconds. The assumption here is that early stages of neurodegeneration could be detected and differentiated from normal ageing as alterations in the dynamical repertoires that the brain networks explore, either at rest or during task performance. These alterations would be reflected either in terms of the probability of the brain switching between network configurations, the duration it spends in particular configurations, or in terms of the sequence or path of configurations. In this talk will advantages and disadvantages of current tools and present a conceptual framework for modelling brain dynamics that bridges between bottom-up data driven models and top-down biophysical models.

How the Human Connectome sustains Multiple States

Patricio Orio[1], Javier Palma-Espinosa[1], Samy Castro[1], Carlos Coronel[1].
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Multi-stable behavior of the brain dynamics is actively being studied as a landmark of ongoing (resting) cerebral activity, reported in both fMRI and M/EEG recordings. This consists on a continuous switching between different partially synchronized states, in the absence of external stimuli. Multi-stability is thought to be an important mechanism for dealing with sensory novelty and to allow for efficient coding of information in an ever-changing surrounding environment. There is some understanding about how network topology, connection delays and noise can contribute to building this dynamic, but a systematic exploration of the interplay between these factors is still missing. We are studying the emergence of dynamical Functional Connectivity (dFC) in simulations of biophysically inspired neurons and neural masses, and how it emerges from local dynamics (chaotic and stochastic), as well as from topological features. In deterministic simulations, the networks show multi-stable dynamics in a certain range of global connectivity strength. When the network is composed of nodes that have chaotic dynamics, we observe a richer dFC with more and more diverse states. Introducing moderate noise into the dynamics enhances the multi-stable behavior, resulting in more heterogeneous synchronization patterns, while more intense noise abolishes multi-stability. In networks composed of nonchaotic nodes, moderate noise can induce multi-stability in an otherwise synchronized, nonchaotic network. Finally, our exploration with different networks topologies reveals that modular (segregated) networks promote multistability; as the connectivity approaches a random pattern the network is more easily synchronized loosing the ability to sustain multiple states. Simulations with a large-scale mean field model show that the Human Connectome contains a core of nodes that facilitate the appearance of multiple states, enabling a richer dynamic. This core of nodes is the first to engage in a high activity state and the rest of the network is engaged in a gradual fashion allowing for multiple network configurations. Our results aim towards understanding the origins of the dFC, enabling a fine tuning of the dynamics in artificial systems and dealing with neuropathologies associated to the disruption of dFC.

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From molecules to consciousness: towards an integrative neuroscience of psychedelic action in the human brain

Enzo Tagliazucchi[1].
(1) Departamento de Física, Universidad de Buenos Aires

Suppose someone consumes a typical dose of lysergic acid diethylamide (LSD). The molecules are absorbed by her body and cross the blood-brain barrier, finally interacting with proteins located at the cell membrane (receptors). Depending on the receptor and the type of interaction with the LSD molecule, different intracellular second messengers are recruited, which in turn modify the biophysical properties of the cell and influence its activity. The next two facts we know about are that the contents of her consciousness are deeply modified, and that such modifications are related to changes in brain activity, as measured with tools such as fMRI, EEG and MEG. But what happened in between? Currently, we have knowledge about the two ends of the process, but how can we connect both ends? In my talk I will move between theory and experiment to propose a way to link scales based on the following assumptions: 1. That it is possible to map the state of the brain (at different scales) into a space with a distance function or metric (i.e. there is a notion of the proximity between two states), 2. That it is possible to map the contents of consciousness into a similar space, and 3. That it is possible to investigate how the distance functions from both spaces relate to each other, e.g. does “being close“ in one space imply “being close“ in the other?

Exploring information-theoretic high-order effects of LSD in a Whole-Brain Model

Rodrigo Cofre[1], Ruben Herzog[2].
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(2) CINV, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, CL

What allows the brain to be more than the sum of their parts is not in the nature of the parts, but in the structure of their interdependencies. High-order interdependencies are increasingly being used in computational neurosciences to characterize interactions between groups variables, often with an emphasis on synergistic and redundant interactions. A promising novel information-theoretic tool has been proposed recently called “O-information” [1]. This function is the first symmetric quantity that can give an account of intrinsic statistical synergy in systems of more than three variables, allowing to asses high order interdependencies. The O-information captures the dominant characteristic of multivariate interdependency, distinguishing redundancy-dominated scenarios where three or more variables have copies of the same information, and synergy-dominated systems characterized by high-order patterns that cannot be traced from low-order marginals. In this talk, I will report on recent progress in quantifying multivariate interdependency in the BOLD signals generated using the Whole-Brain Multimodal Neuroimaging Model proposed in [2] under two scenarios. First, without serotonin neuromodulation (placebo condition) and including the neuromodulation to mimic the LSD condition. We discuss our results in the context of the “entropic brain” hypothesis [3], which states that the richness of experience reported during the LSD and other psychedelics condition correlates with signal diversity which can be characterized by the entropy of the signals. We argue that the “richness of content” expected in brain signals generated under the psychedelic experience can be characterized through high-order interdependencies among brain modules by means of the O-information.

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Cholinergic modulation of neuronal excitability: role of TRPM4 channel. holinergic modulation of neuronal excitability: role of TRPM4 channel

Elias Leiva[1].
(1) Biología, Química y Biología, Universidad de Santiago

Medial prefrontal cortex receives cholinergic inputs from basal forebrain and local inputs from interneurons in the layer 1 which shapes its electrical properties. This cholinergic modulation specifically targets different cortical layers, the neurons wherein express different cholinergic receptors, giving an increasing processing and control capabilities of the cortical excitability. Intracellular Ca^{2+} is critical for this process and is actively involved in the setting of the resting membrane potential and particularly in medial prefrontal cortex layer 2/3, pyramidal neurons express TRPM4, a non-selective cation channel permeable to monovalent cations and activated by intracellular calcium with a somatic and proximal-dendritic distribution. Using slice electrophysiology and local perfusion of pharmacological modulators of TRPM4 and cholinergic receptors, we study the participation of TRPM4 in modulation of local membrane potential in response to cholinergic modulation and how this impact the EPSP transmission. We found that somatic carbachol perfusion depolarizes layer 2/3 neurons, TRPM4 inhibition reduces this effect. Furthermore, the application of TRPM4 inhibitor obliterates the effect of carbachol on mEPSP. Additionally, after a train of synaptic stimulation, the application of TRPM4 inhibitors in the soma or in the distal dendrites obliterates the effect of carbachol in the eEPSP amplitude and slope. Altogether, our results suggest that TRPM4 participates in the cholinergic control local excitability with ensuing effects on synaptic transmission

FONDECYT 1181814

Role of TRPM8 channels in altered cold sensitivity of corneal primary sensory neurons induced by axonal damage

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The cornea is extensively innervated by trigeminal ganglion cold thermoreceptor neurons expressing TRPM8. These neurons respond to cooling, hyperosmolarity and wetness of the corneal surface. Surgical injury of corneal nerve fibers alters tear production and often causes dry eye sensation. The contribution of TRPM8-expressing corneal cold-sensitive neurons (CCSNs) to these symptoms is unclear. Using extracellular recording of CCSNs nerve terminals combined with *in vivo* confocal tracking of re-innervation, Ca^{2+} imaging and patch-clamp recordings of fluorescent retrogradely labeled corneal neurons in culture, we analyzed the functional modifications of CCSNs induced by peripheral axonal damage in male mice. After injury, the percentage of CCSNs, the cold- and menthol-evoked intracellular [Ca^{2+}] rises and TRPM8-current density in CCSNs were larger than in sham animals, with no differences in the brake K^+ current I_{KD}. Active and passive membrane properties of CCSNs from both groups were alike, and corresponded mainly to those of canonical low- and high-threshold cold thermoreceptor neurons. Ongoing firing activity and menthol-sensitivity were higher in CCSN terminals of injured mice, an observation accounted by mathematical modeling. These functional changes developed in parallel with a partial re-innervation of the cornea by TRPM8(+) fibers and with an increase in basal tearing in injured animals compared to sham mice. Our results unveil key TRPM8-dependent functional changes in CCSNs in response to injury, suggesting that increased tearing rate and ocular dryness sensation derived from deep surgical ablation of corneal nerves are due to enhanced functional expression of TRPM8 channels in these injured trigeminal primary sensory neurons.

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The phosphorylation of the TRPV1 channel mediated by the Cdk5 kinase increases its function in trigeminal sensory neurons

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Orofacial pain has a complex etiology and is associated with several diseases that include neuralgias, pulpitis, migraine and headaches, and temporomandibular disorders, among others. The inflammation of these tissues is implicated in many of these pathologies. Inflammatory mediators secreted by damaged tissue and immune cells regulate many signal transduction cascades that increase the activity of certain kinases, leading to nociceptor sensitization and a consequent enhancement in pain sensation. We reported earlier that peripheral inflammation increases cyclin-dependent kinase 5 (Cdk5) activity, an important protein involved during orofacial pain signaling. Cdk5 is a serine/threonine kinase mainly active in post-mitotic neurons whose function is essential for the proper development and function of the brain. We also demonstrated that Tumor Necrosis Factor-alpha (TNF-a), or Transforming Growth Factor beta 1 (TGF-b1), two important cytokines involved in orofacial pain, are able to increased Cdk5 kinase activity mainly by up-regulation of p35 protein, an activator of Cdk5. At molecular level, Cdk5 phosphorylate important receptor channels of noxious stimuli such as Transient Receptor Potential Vanilloid 1 (TRPV1), Transient Receptor Potential Ankyrin 1 (TRPA1), and purinergic P2X receptor (P2X2R), among others. Thus, Cdk5-dependent phosphorylation of TRPV1 at threonine 407 results in increased of Ca+2 influx in sensory trigeminal neurons, which in turn increment pain perception, suggesting that Cdk5 might be a new therapeutic target for the treatment of inflammatory orofacial pain.

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Molecular determinants of cold-evoked responses in mouse vagal sensory neurons

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Transient receptor potential (TRP) channels are known for being crucial molecular sensors for chemical, mechanical and thermal stimuli. Two TRP channels have been shown to participate in cold sensing. TRP Melastatin 8 (TRPM8) is a well-established sensor for mild cold. TRP ankyrin 1 (TRPA1) is a polymodal chemosensor of irritant stimuli, with a somewhat controversial role in noxious cold sensing. Both channels are expressed in various tissues, including non-overlapping subpopulations of peripheral sensory neurons innervating the skin and surface epithelia (e.g. the cornea). Here they sense decreases in temperature, giving rise to neural activity that is processed for discriminative and thermoregulatory behaviors. However, responses to cold stimuli are also found in visceral neurons innervating internal organs, where their function as cold sensors may not be as obvious as in somatosensory neurons. The aim of this study was to investigate and characterize the responses to cold temperature in visceral vagal neurons. For this, we isolated neurons from the nodose ganglia (NG) from 6-8 weeks old male wild-type or genetically modified mice. Neurons were enzymatically and mechanically dissociated, cultured and used for calcium imaging experiments within 24 hours. Neurons were incubated with the calcium indicator dye Fura2AM and excited at 340 and 380 nm wavelengths to measure intracellular calcium levels. Cold ramps from 33 to 11 ºC were applied to cells in the presence or absence of TRP channel antagonists followed by various other TRP channel agonists. In visceral neurons from wild type mice ~ 20 % of neurons responded to a decrease in temperature and ~ 75 % out of these cold responders were also activated by the selective TRPA1 agonist allyl isothiocyanate (AITC). Moreover, these cold responses were reversibly reduced by two different TRPA1 antagonists: HC030031 or A967079. The mean temperature threshold of responders to cold was 18 ± 0.5 ºC (n=115). In neurons from TRPM8 KO mice, the number of responders to cold was maintained at 17 % of cells; however, in neurons from TRPA1 KO or TRPA1/TRPM8 double KO mice, cold-activated neurons were reduced to 5 and 6 %, respectively. In NG from a TRPM8-EYFP transgenic mouse only around 3 % of neuronal profiles were highly EYFP positive. This modest expression of TRPM8 is likely derived from the jugular ganglion. This shows that TRPA1 channels are the main mediator of cold responses in visceral vagal neurons. Our data also show that there are additional cold-sensing mechanisms, independent of TRPM8 or TRPA1, accounting for the remaining 5 % of cold responders in the vagal ganglion complex.

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“Neuroscience of bistable stimuli: a window to brain function”

Chair: Pedro Maldonado

Brief periods of gamma enhancement correlate with sustain perception

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In natural vision visual percepts stand for long periods of time, in the order of seconds or minutes. In contrast, most of our knowledge of the neural correlates of visual processing comes from brief presentation of visual stimuli, around 200-500 ms. In this context, visual bistable stimuli trigger sustain perceptual states that last 3-4 second, given the opportunity to study the neural correlates of sustain perception. Here, I’ll show the results from a series of experiments recording electroencephalography and eye movements from volunteers that look at the Necker cube, and manipulations of this task. Subjects freely move their gaze over the stimulus and they report the changes in perception by pressing a button. Mainly, we observed a spatially broad but temporally brief increment in gamma activity 800 ms before manual report, and a later modulation of alpha band activity. I’ll discuss the role of parieto-occipital alpha modulation on this perceptual task, the role of gamma activity on the change of perception and its relation with eye movements. We’ll also discuss the implications of these results for visual perception, particularly for active sensing.

ICM P09-015F

Top-down or bottom-up causes perceptual changes in bistable stimuli?

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During bi-stable perception, subjects report the alternation between different percepts, although the stimulus remains physically invariant. However, eye movements occurring while viewing these images can cause changes in the retinal input, thus affecting perception. To determine whether eye movements affect perceptual alternation during the bi-stable stimulus, we examine the eye movement behavior of 27 subjects while recorded their perceptual transition reports. Subjects either fixate on a point on the screen or freely view the stimulus. In another condition, we also asked the subjects to either avoid or force perceptual transitions.

We found no temporal association of eye movement occurrence and the perceptual report, neither the amplitude or direction of these eye movements. However, when subjects were instructed to force perceptual transitions, the number of eye movements increase compared with free viewing or when they avoid transitions. We also did find that the occurrence of saccades shows an oscillatory pattern, that coincides with the temporal changes in electroencephalographic activity, which is characteristic of previous reports on perceptual changes in bi-stable stimulus. These results suggest that ocular movements do not participate in neural mechanisms related to the perceptual switch.Funded by ICM P09-015-F

Perceptual bistability as probabilistic inference

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Despite the apparent stability of perception, many perceptual decisions are made in the presence of ambiguity or noise, like when we drive a car in the night or in the fog. Because of this stimulus uncertainty, the brain needs to combine different sources of information with prior information about the statistics of the world. A long-standing problem is determining how the brain integrates these sources of information. I will review our experimental and modeling results on the dynamics of the brain in bistable perception (e.g., the Necker cube) and decision making in the face of uncertainty. Our results from cue combination experiments suggest that the brain represents probability distributions over the causes of the stimulus, and that the dynamics of perception arises from a sampling process of that probability distribution. I will describe diffusion models embedded in double-well potentials, known to perform Langevin Monte-Carlo sampling, as well as biophysically realistic networks that generate the observed behaviors. Our results invite us to explore the hypothesis that the brain is an approximate inference machine that represents probability distributions and uses similar neuronal principles throughout domains to solve tasks in the face of uncertainty.

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Perceptual bistability a case study for free will?

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Bistable or multistable perception happens when an appropriately ambiguous sensory stimulus is presented to the subjects. The ambiguity of the stimulation leads to an unstable perceptual interpretation, such that perception cannot settle on a single perceptual object, but itinerate between the two or more perceptual objects compatible with the sensory stimulation. Multistable perception has been extensively studied as a paradigmatic example of neural activity self-organization. Here we will dwell on multistable perception as a model to experimentally approach the concept of agency and free will. We will argue that data on multistable perception support a weak notion of agency and free will, understood as an autonomous conscious control of cognitive states.

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A serotonergic dysfunction precedes and contributes to the onset of motor symptoms in a *Drosophila* model for Parkinson´s Disease

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Parkinson's disease (PD) is a degenerative disorder characterized by several motor symptoms (MS) including shaking, rigidity, slow movement and difficult walking, and also non motor symptoms (NMS) which include olfactory dysfunction, depression, anxiety and sleep disorders. Although PD is characterized by a progressive loss of dopaminergic neurons, there are other neural systems affected including the serotonergic system. Understanding the timing at which neurochemical, MS and NMS occur could provide new insights on the determinants of the disease. This is one of the objectives of the work carried out in our research group. In doing this, we use a well-known *Drosophila* PD model generated by a deletion in the fly PINK1 gene (PINK1^{B9}). We have carried out a thorough study of the timing at which neurochemical and behavioral changes occur in the PINK1^{B9} mutant flies. Thus, we have been able to define that the onset of MS associated to PD occur only by the third week of age in adult flies. This helped us define symptomatic and presymptomatic phases in this animal model for PD. Interestingly, during the presymptomatic phase we were able to describe an olfactory alteration which is reminiscent of what is described in up to 95% of PD patients. Moreover, we described changes in the dopaminergic system that occur before the onset of motor alterations, suggesting compensatory mechanisms that delay the onset of MS in this PD fly model. During the pre-symptomatic phase in the PD fly model, we have also discovered a lower brain serotonin content and defects in the serotonin transporter activity. These changes in the serotonergic system precede the alterations in the dopaminergic system. Thus, we proposed that an early dysfunction in the serotonergic system during the pre-symptomatic phase in this PD fly model contributes to the Parkinsonian phenotype. We tested this hypothesis by artificially increasing the serotonergic signaling in young PINK1^{B9} flies. This treatment partially prevented the onset of locomotor defects commonly associated to the fly PD model. Thus, we propose that the serotonin signaling in young flies is important for the adequate operation of neural circuits responsible for planing and/or execution of motor programs.
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Communication and plasticity within the circadian network: a role for the BMP signaling pathway

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Rhythmic rest-activity cycles are controlled by an endogenous clock. In *Drosophila*, this clock resides in about 150 neurons organized in clusters whose hierarchy appears to change in response to environmental conditions. In the absence of external cues the LNvs play a key role as they set the phase of several other clock neurons and thus sustain the temporal organization of behavior. To improve the understanding about the communication among different circadian clusters we carried out a miss-expression screen in the LNvs. This approach uncovered a role in period determination for the BMP signaling pathway, a highly conserved retrograde pathway that influences synaptic connectivity through transcriptional control. Most subsets of circadian neurons express a single ligand, *activin b*. However, the LNvs express different combinations; both small and large LNvs release DPP. Interestingly, DPP overexpression in the LNvs triggered a period lengthening phenotype, while its downregulation caused reduced rhythmicity, underscoring this ligand *per se* conveys time-of-day relevant information. To uncover the contribution of each specific subset we took advantage of the power of *Drosophila* genetics. DPP expression in the small or large LNvs elicited opposite effects on period length. Accordingly, acute (short term) deregulation impairs circadian remodeling of axonal terminals, likely through local modulation of the guanine nucleotide exchange factor (GEF) Trio. These findings open the provocative possibility that the BMP pathway is recruited to strengthen/ reduce the connectivity among specific circadian clusters and thus modulate their contribution to the circadian network.

Acadvl-regulated lipid oxidation modulates neurodegeneration in *Drosophila*

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The increase in life expectancy of the population observed over the last years has amplified the relevance of neurodegenerative diseases. The decay of neuronal structures triggered by aging-linked mechanisms such as misregulated proteostasis and metabolism, is particularly visible in fragile compartments as the axon. Neuronal degeneration initiated in the axon is a convergent phenomenon named dying back mechanism, which has been associated to pre-symptomatic stages of several neurodegenerative diseases including Amyotrophic lateral sclerosis (ALS). The molecular basis of selective destruction of axons is not yet completely elucidated, but it is known that mitochondria play a central role on it. To further explore the role of mitochondria in axonal degeneration, we used a model of axonal injury in the *Drosophila* wing to genetically modulate the expression of mitochondrial proteins linked to metabolism. We found that Acadvl, which catalyzes the first step of lipid oxidation, significantly delays axonal degeneration when down-regulated. Involvement of lipid metabolism on this phenotype was confirmed with independent alleles, modifying the expression of other 16 related proteins from the pathway, and feeding flies a high-fat diet. Then, we aimed to analyze whether differential expression of Acadvl alters neurodegeneration on a model expressing the dipeptide repeats (DPR) linked to the ALS-causative gene C9orf72 in the fly nervous system. We observed that down-regulation of Acadvl enhances the DPR-linked toxicity when expressed in the eye, and the opposite phenotype was seen when the same gene was over-expressed. Furthermore, Acadvl showed a potential effect on aging as down- and over-expression of this gene strongly decreases and increases flies lifespan, respectively. These data suggest a novel role of Acadvl and lipid oxidation in neurodegeneration and aging, and therefore we plan to discuss potential mechanisms and metabolites involved.

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Glucose metabolism in the brain under low and high activity: importance of the glia and lactate transport

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Neural activity demands high energy to sustain cell physiological processes. As an extreme case, the human brain requires the highest amount of energy as compared to other organs on an equal mass basis. Thus, the brain spends 20% of the body energy despite the fact that its mass is only 2% of the whole body. The main locus of energy demand is the synapse, in which the recycling of synaptic vesicles and the maintenance of the ionic gradients (mainly in the postsynaptic compartments) are the most energy-demanding process. The function of the brain depends mainly on mitochondrial oxidative phosphorylation (ox-phos). It is known, however that glial cells in the brain depend more on glycolysis while the energy metabolism in neurons is mainly based on ox-phos. The characteristic energy metabolism of neurons implies that pyruvate derived from glucose oxidation through glycolysis enters the mitochondria, where it is in turn completely oxidized. Pyruvate production depends on the transport of glucose from the extracellular and its conversion to pyruvate through glycolysis. Pyruvate in turn, can be converted to Lactate by the enzyme lactic dehydrogenase. It is apparent, however, that during high demand neurons can use substrates other than glucose to obtain energy. These molecules comprise monocarboxylic acids like L-lactate, pyruvate and ketone bodies. Most attention has been focused on lactate and the hypothesis of the astrocyte-neuron lactate shuttle (ANLS), which proposes that Lactate transported from glial cells to neurons is necessary to sustain the high energy demand that neuronal activity requires. However, the in vivo mechanisms and characteristics that underlie the transport of monocarboxylates (MCT) are poorly described. Additionally, the generality of this mechanism has not been demonstrated. Using Drosophila expressing genetically-encoded FRET sensors we explored the MCT in motor neurons and glial cells from the larval ventral nerve cord in an ex vivo model. We will show that lactate/pyruvate transport on glial cells is coupled to protons and that glial cells maintain higher levels of intracellular lactate generating a positive gradient towards neurons. Interestingly under high neuronal activity, increases of lactate on motor neurons depend on the transfer of lactate from glial cells mediated in part by the previously described monocarboxylate transporter Chaski, giving support to the in vivo glia-to-neuron lactate shuttling during activity.

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Brain Changes in Age-Related Hearing Loss

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Age-related hearing loss is associated to cognitive decline and has been proposed as a risk factor for dementia. However, the mechanisms that relate hearing loss and cognitive decline remain elusive. Here we propose that the impairment of the cochlear amplifier and of auditory nerve function are associated to structural brain changes and cognitive impairment in elderly subjects. Methods: The ANDES (Auditory and Dementia study) project is a prospective cohort of Chilean hispano-mestizo elders ≥65 years, "cognitively" normal (MMSE>24) with different levels of age-related hearing impairment. A total of 101 people have been evaluated with comprehensive neuropsychological and audiological evaluations, including: audiometric thresholds (0.25 to 8 kHz), amplitudes and latencies of auditory brainstem responses (waves I and V obtained at 80 dB nHL), and distortion product otoacoustic emissions (DPOAE). Results: 101 participants (64 women) complied with the inclusion criteria, with a mean age of 73.5 ± 5.2 years, and a mean education of 9.5 ± 4.2 years. The average audiogram thresholds for the better ear was 25.5 ± 12.1 dB HL, while average MMSE was 28.1 ± 1.3.The group with cochlear amplifier dysfunction showed greater brain atrophy in the cingulate cortex and in the parahippocampus. In addition, the atrophy of the cingulate cortex was associated with cognitive impairment in episodic and working memories, and in language and visuoconstructive abilities. In addition, we found significant correlations between the Trail Making Test A and the amplitude of wave I (r= -0.272; p= 0.007), and between Boston nomination test and the latency of wave V (r=-0.208, p=0.039). These results suggest that the dysfunction of different auditory structures are associated to alterations in different brain structures and cognitive domains.

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Encoding of behavioral meaning of sounds in a tertiary area of the ferret auditory cortex

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The mechanisms by which the brain integrates acoustic feature information with internal representations (such as behavioral goals, expectations and memories of previous sound-meaning associations) and links them with appropriate audio-motor responses is currently unknown. In order to better understand how the brain performs this task, we recorded auditory responses in a newly described tertiary area, the Rostral-Ventral Posterior field (VPr) of the Posterior Ectosylvian Gyrus (PEG) from four ferrets performing auditory discrimination tasks. Neurons in primary auditory cortex (A1) of the ferret have been shown to undergo rapid task-related plasticity of spectrotemporal receptive fields (STRFs) in order to enhance their ability to encode task-relevant sounds during performance of auditory tasks requiring discrimination between stimuli belonging to different behavioral categories. We have also shown that the representation contrast between task-relevant sounds is further increased in non-primary auditory cortical areas in the dorsal PEG (dPEG). Previous findings in the dorsolateral Frontal Cortex (dlFC) are consistent with a model in which top-down signals from the frontal lobe coding for abstract stimulus meaning can modulate auditory cortex plasticity. However, it is currently unknown how and where in the brain veridical acoustical information integrates with top-down abstract information. Our results reveal that neurons in VPr, while being responsive to auditory stimuli, can greatly enhance the contrast between sound representations belonging to different behavioral categories, similar to dlFC neurons. Furthermore, VPr shows increased responses during passive listening to behaviorally-relevant target stimuli in trained compared to task-naïve animals, which suggests long-term learning. This selective enhancement to target stimuli is further amplified during active performance of auditory discrimination tasks. VPr neurons also show long sustained short-term memory activity after target stimulus offset, correlated with task response timing and action - a type of persistent response we previously reported in dlFC neurons. These rapid task-related changes in activity and filter properties enable VPr neurons to quickly and nimbly switch between different responses to the same acoustic stimuli in different behavioral contexts, reflecting either the timing or spectrotemporal properties or behavioral meaning of the sound. Furthermore, they demonstrate an interaction between the dynamics of long-term learning and short-term attention as incoming sound is selectively attended, recognized and translated into action.

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Attention and Emotion in Tinnitus: Insights from Functional MRI”

F Husain[1].
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Patients with tinnitus are highly heterogeneous, varying in terms of etiology, type and laterality of sound being perceived and severity of their psychological reaction to the chronic sound. In this talk, I will review the latest research, from our lab and from other centers, about the neural correlates of tinnitus perception and an individual’s psychological reaction to it. The major dimensions along which the psychological reaction varies are audition, emotional processing and attention. Brain imaging, specifically task- and rest-based functional MRI, are excellent tools to study the functional properties of the neural networks involved in auditory and extra-auditory processing. In particular, resting state fMRI allows us to probe the short-term condition of state of tinnitus perception as well as long-term psychological traits. I will end the talk with a potential model of habituation, that of the attention system (via the frontal cortex) suppressing the response from the emotion processing network (via the limbic system). Department of Defense, USA

Deviance detection along the auditory neuroaxis and beyond: A neuronal correlate for predictive coding?

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S*timulus-specific adaptation (SSA)* is the reduction in the responses to a common sound relative to the same sound when rare. It was originally described in the primary auditory cortex (A1) as the neuronal correlate of the mismatch negativity (MMN), an important component of the auditory event-related potentials that is elicited by changes in the auditory environment. However, the relationship between SSA and the MMN is still a subject of debate. The MMN is a mid-late potential (~150-200 ms in humans), and its neural sources have been located mainly within non-primary auditory cortex in humans and animal models. Moreover, SSA is also present as early as in the auditory midbrain and thalamus (IC and MGB).

In this talk, I will show our recent findings on recordings from single neurons in the IC, MGB and auditory cortex (AC) of anaesthetized rats and awake mouse to an *oddball* paradigm similar to that used for MMN studies. Our data demonstrate that most neurons in the non-lemnical divisions of the auditory brain show strong SSA and that there is a hierarchical emergence of prediction error signals along the central auditory system. Recordings from prefrontal cortex show that neurons exhibit the highest degree of prediction error along the auditory hierarchy. We have also observed that acetylcholine seems to play a role in shaping SSA by differently affecting the response to the standard or deviant tones sounds only in IC or AC, respectively.

Taken together our results unify three coexisting views of perceptual deviance detection at different levels of description: neuronal physiology, cognitive neuroscience and the theoretical predictive coding framework.

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The Design, Distribution, and Use of Open Source and Low Cost Tools for Science

Chair: Timothy Marzulo

It's not open source unless someone else can build and use it! Lessons on how to effectively share your inventions

Timothy Marzulo[1].
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The advantage of open-source invention is that other users, by properly examining the schematics, can build and modify the designs per the necessities of their experiments. Extensive documentation, often the least exciting and most tedious part of the invention process, is fundamentally necessary for an invention to be truly "open source." Test cases of ideal and non-ideal documentation inventions will be shown, using examples from our research group on open-source amplifiers, stimulators, and microscopes. More ideal examples outside of our research group, such as Arduino, will also be discussed as well as non-ideal examples. By the end of the seminar the audience will have a sound background on what separates the merely average and prosaic from the excellent open source inventions.

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Open Source Technology for Research and Education in Biological Sciences and Bioengineering

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The high costs of proprietary scientific tools and the restrictions imposed to their inspection, distribution and customization can be detrimental to the equitable production of knowledge, education and civic action. Open source hardware addresses these problems by allowing the engineering of scientific instruments whose design files can be openly shared, studied and improved under free/libre open source licenses. The advent of easy-to-use microcontrollers, off-the-shelf electronics and digital manufacturing technology has further facilitated the crowdsourced and distributed production of scientific hardware worldwide. We embrace this view and work on the development of open resources for research and teaching; ranging from molecular biology tools to open scientific hardware. In this talk, we will share the work of GOSH (Global Open Science Hardware), an international and diverse community that promotes the freedom to use, study, replicate, adapt, distribute and sell scientific instrumentation. We will also describe our work on open hardware devices for low cost microscopy, fluorescent imaging and DNA detection as well as open genetic tools for DNA assembly. Finally, we will briefly discuss current efforts to promote the development and adoption of open source technologies in Latin America.

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Case study: Using Open Source Tools to Quantify Cockroach Locomotion

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More than 50 years ago a small revolution takes place in Chile. In a small laboratory in Santiago, Dr. Joaquin Luco showed that when he amputated the front leg of the cockroach, the insect must learn to balance in the remaining legs to realize the simple task of cleaning its antenna. Dr. Luco observes that this simple learning process is accompanied by an increase in the probability of discharge of the ganglia that control the remaining legs, showing for the first time, a correlation between a physiological and a learning process. By that time, the electrophysiological recordings were difficult and require a deep knowledge of analog electronics, also the analysis of the data was difficult and lack of the nowadays precision. In our study, we use the advantage of opensource tools to recreate the experiments of Dr. Luco and study insect motor learning, an active field oriented to the development of motor control algorithms. In our experiments, we detect adaptational changes that allows the animal to maintain a certain velocity due to the compensation of march parameters, compensation that was accompanied by a change in ganglion discharge. In our days, the development of commercial solutions has increased the reliability of the electrophysiological and behavioral tools, but the high prices of those solutions still hinder thats experiments for laboratories with reduced budgets. If well still is necessary to increase the literacy in software programming and digital electronics, the use of opensource devices and software, appears as a cheap and accessible tool, offering new personalized solutions for the scientist, boosting the creativity thought innovative approximations that could be easily validated by commercial software and readily shareable with the scientific community.

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Designing your own two-photon microscope and optic systems: The power of freedom under design and budget constraints

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The development of genetically encoded calcium and electrical activity sensors, together with recently developed microscopy and optical tools, allow us to record neuronal/glial activity in live anesthetized or awake animals Main constraints with these new optical tools - particularly in countries where resources are limited-, are the associated monetary costs; the delayed, expensive and sometimes inexistent technical support; and the lack of setup flexibility of commercially available equipment. These issues restrain our ability to innovate and perform new experimental designs and tasks. Most of these problems could be solved by using open-source tools, 3D-printed parts, and the bidirectional support with companies/organizations that embrace a policy of “do it yourself”. Using two-photon microscopy and photometry as example, the purpose of this work is to present the feasibility of building these setups in Chilean institutions, share knowledge of available open-source tools, present laboratory teams seeking collaborations, and discuss the importance of these research approaches for the development of Chilean neuroscience.

Protocol for suppression of phase synchronization in Hodgkin-Huxley-type networks

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Phase synchronization of neurons is fundamental for the functioning of the human brain which can be related to neurological diseases such as Parkinson and/or seizure behaviors generated by epilepsy. For small-world networks, an atypically high level of phase synchronization may occur even for unexpected low values of the coupling strength when compared to traditional critical values which delimit the transition from a globally stable unsynchronized to a globally stable phase synchronized states. This regime is characterized by a non-monotonic transition as a function of the coupling parameter. In order to study this phenomenon, we consider a neural network composed of 5,000 Hodgkin–Huxley-type neurons, coupled by a small-world connection matrix. Based on suppression protocols of phase synchronization, we study how this abnormal phase synchronization can be suppressed by applying an external pulsed current in the network. It is shown that the synchronization for weak coupling can be suppressed without any visible effect in the globally stable asymptotic state occurring for higher values of the coupling strength. We also demonstrate that to preserve the unsynchronized state, the external current must be kept switched on, otherwise, the abnormal synchronization regime is recovered due to the globally stable state present on the dynamics. Optimization protocols are studied by varying the amplitude and time intervals of the current pulses.

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Axonal signaling endosomes mediates dynein-dependent long-distance dendritic branching by activating PI3K-mTOR local translation in cell bodies

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Brain Derived Neurotrophic Factor (BDNF) is broadly express in many circuits of the central nervous system (CNS). It binds the receptors TrkB and p75 to trigger different signaling pathways, including ERK1/2, PLC-gamma and PI3K-mTOR, increasing dendritic growth and regulating synaptic plasticity. When binding to BDNF, TrkB and p75 are endocytosed to signaling endosomes, organelles that participates in intracellular signaling and communication. Whether BDNF/TrkB-p75 signaling endosomes participates in long-distance signaling from axons to cell bodies is unknown. Here, we studied the functional role of BDNF/TrkB-p75 signaling endosomes and BDNF signaling pathways in long-distance regulation of dendritic growth using compartmentalized cultures of rat and mouse cortical neurons derived from p75 NTR knock out or TrkBF 616A knock-in mice. By applying BDNF to distal axons, we showed that TrkB but not p75 activation was required to increase dendritic arborization process that was dependent on transcription factor CREB and the PI3K-mTOR pathway in cell bodies increasing protein synthesis. On the other hand, the endosomal regulator Rab5 and the molecular motor dynein were required for these effects, suggesting the requirement of endosomal pathway for BDNF long-distance signaling. Our results suggest a role for long-distance BDNF-TrkB signaling endosomes wiring circuits in the CNS.

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Binding objects into a mental array: Neurophysiological correlates of sequential visuo-spatial working memory

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Working memory (WM) has a central role in human cognition allowing us store and manipulate information to perform a wide range of complex tasks. For instance, reading comprehension requires dynamically combine new information with the stored one in WM. However, it remains unclear how new incoming information is sequentially integrated into WM mental representations, especially in the visuo-spatial modality.

We designed an experiment in which participants must maintain in memory three sequentially presented items, integrate them into a mental array, compare it with a test array and report differences. Behavioural performance and EEG neural signal were measured during each session.

We found that after the first item was stored in WM,

ORAL COMUNICATIONS I

Epigenetic Modifications and Neuronal Function: Insights from the Ryanodine Receptor-3

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Transcriptional changes nourish the dynamic nature of the neural function. Experience-dependent gene expression lies at the basis of the functional and structural plasticity of neurons, contributing to complex cognitive phenomena, such as learning and memory. Epigenetic modifications allow the adaptation of chromosomic regions to register, signal or perpetuate altered states of activity. Hence, it is relevant to understand how epigenetic changes are related to experience-dependent gene expression and to which extent these epigenetic marks contribute to neuronal function and dysfunction. The ryanodine receptors are intracellular calcium channels that, through calcium-induced calcium release, contribute to hippocampal long-term potentiation and learning and memory. Using enriched environment and training in the Morris water maze, we have strengthened the relationship between DNA-methylation and DNA-hydroxymethylation in directing the transcriptional activity of the ryanodine receptor 3 in response to experience. Moreover, we have related these DNA modifications to the methylated cytosine binding protein 2 (Mecp2) and hippocampal dendritic spine remodeling, extending our observations to a neurodevelopmental disorder known as Rett syndrome (RTT). Our observation suggests that the dynamic expression changes of ryanodine receptors associated with early-postnatal development are lost in an RTT mouse model, suggesting a role for these channels in the pathophysiology of this devastating disorder. Altogether, our observations highlight the role of DNA modifications for physiological and experience-induced changes in gene expression. At the same time, our observations provide a functional link to understand a devastating pathological condition, calling for attention to the role the epigenome plays in physiological and pathological conditions.

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Episodic hypercapnic stimulation of central chemoreceptors induced respiratory plasticity and elicits long-term breathing disorders in heart failure rats

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Enhanced central chemoreflex (CC) gain is observed in heart failure (HF) and it is relatedwith breathing disorders and autonomic dysfunction. Episodic hypercapnic stimulation (EHS) epochs may result from apneas/hypopneas events which are largely increase in HF. Therefore, it is possible that EHS may serve as a substrate to maintain enhanced CC gain and perpetuates breathing disorders in HF.We sought to determine whether EHS contributes to cardiorespiratory dysfunction in HF and its dependence on central chemoreceptor neurons.HF was surgically induced by volume overload in male Sprague-Dawley rats. Indwelling radiotelemetry wasimplanted for blood pressure monitoring. Upon recovery, rats were exposed to episodic hypercapnicstimulation (EHS, 10 cycles of 5 min FiCO27%) in a plethysmograph chamber for measure cardiorespiratory function. To determine the contribution of CC, partial ablation of chemoreceptor neurons within the retrotapezoid nucleus (RTN) was performed via anti-subastance P-conjugated saporin toxin (SSP-SAP) injections.Vehicle treated rats (HF+Veh and Sham+Veh) were used as proper controls for SSP-SAPexperiments. Ventilatory long-term depression was observed in all animals 60 min post-EHS, being negligible in HF ($\Delta\dot{V}E$-5.5 ± 0.9 vs. 1.2 ± 0.6 mL/min/100g, Sham+Veh vs. HF+Veh, $p<0.05$). Furthermore, EHS resulted in autonomic imbalance, cardiorespiratory entrainment, and ventilatory disturbances only in HF+Veh rats. These effects were markedly attenuated by SSP-SAP treatment in HF rats. Importantly, the apnea/hypopnea index (AHI) was significantly lower in HF+SSP-SAP rats compared with HF+Veh rats (AHI: 5.5 ± 0.8 vs. 14.4 ± 1.3 events/hour, HF+SSP-SAP vs. HF+Veh, respectively, $p<0.05$). In addition, EHS-triggered cardiorespiratory alterations in HF rats was related with augmented respiratory-cardiovascular coupling, that was completely abolished by SSP-SAP injections in the RTN.EHS triggers ventilatory plasticity and elicits cardiorespiratory abnormalities in HF, that arelargely dependent on CC RTN neurons integrity. Also, RTN seems to govern resting ventilatory patterns in HF.

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Traumatic brain injury induces synaptic alterations dependent on the synaptic and ASD-related protein Shank3

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Traumatic brain injury (TBI) might lead to psychiatric disturbances, presumably associated with neuronal loss and/or altered reconstitution of the synaptic connections. At excitatory synapses, Shanks are large scaffolding proteins present at the postsynaptic density. Psychiatric conditions such as Autistic Spectrum Disorders (ASD) have been attributed to mutations in Shank3 gene. This study is aimed to analyze synaptic and behavioral changes in response to TBI in a context of Shank3 loss. Mild TBI was performed in WT and Shank3Δ11(-/-) male mice. Dendritic spines, excitatory synapses, neuronal loss, and the expression of the stress Corticotropin-Releasing-Hormone (CRH) were assessed. Finally, a behavioral analysis was performed to analyze motor, cognitive, and autistic-like features. In WT animals mTBI induced loss of excitatory synapses and dendritic spines in the CA1 and CA3 region of the hippocampus. Interestingly, Shank3Δ11(-/-) mice, despite presenting a lower basal level of dendritic spines and excitatory synapses, were not affected after mTBI. Hippocampal CRH expression was highly upregulated in TBI-WT but not in TBI-Shank3Δ11(-/-) animals, indicating that stress response is altered in these mice. In the open field, TBI-WT mice had anxiolytic or disoriented behavior, while TBI-Shank3Δ11(-/-) mice were unaffected. In the trace-fear conditioning paradigm, only TBI-WT mice displayed an enhanced fear learning. Whereas Shank3Δ11(-/-) mice exhibited an overall enhanced fear learning and an enhanced contextual memory independent of mTBI. Moreover, mTBI did not function as a second hit for ASD in Shank3Δ11(-/-) animals nor induced autistic-like features in WT animals. Therefore, the synaptic alterations observed after TBI are Shank3-dependent since TBI in the absence Shank3 induces an entirely different response at the synaptic and behavioral levels by no worsening of the original phenotype in a knock out-Shank3 model.

CRC 1149

The overexpression of the transcription factor XBP1s reduces the accumulation of Amyloid beta deposits on an experimental model of Alzheimer's disease

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Introduction**:** Alteration of the proteostasis network is an emerging feature of Alzheimer´s disease (AD), where we highlight the occurrence of ER stress and the activation of UPR stress sensor IRE1 and its downstream target, the transcription factor XBP1. A polymorphism in XBP1 promoter was linked to AD and global gene expression profile analysis revealed XBP1 regulates a cluster of AD-related genes. Here we study the contribution of the active form of XBP1 to AD using mouse models. Methods: We used both transgenic mice and gene therapy strategies to overexpress the active form of XBP1 in the brain of the 5xFAD AD mouse model. Animals were analyzed for AD pathological features using histological, biochemical, behavioral and electrophysiological tests. Results**:** We observed a substantial reduction, in the accumulation of amyloid beta (Aβ) deposits in XBP1s/5xFAD mice when compared to 5xFAD mice using 4G8 antibody and aqueous-insoluble Aβ species. Remarkably, these results correlated with improved learning and memory as measured by means of the Morris Water maze test and also LTP measurements. Discussion: Our results demonstrate a functional role of ER proteostasis impairment in AD offering new potential strategies for ameliorating disease pathology.

Glutamate transporters and glutamatergic system in cortical and limbic brain areas in an animal model of depression

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Major depressive disorder (MDD) affects around 10% of the world´s population. Chronic stress results in an increase in extracellular glutamate and dysregulation of the glutamatergic system in brain regions that regulate mood and cognition, which may lead to MDD. However, the mechanisms underlying the abnormal glutamatergic transmission in depression remain controversial. Glutamate transporters regulate the homeostasis of extracellular glutamate levels and thus, its dysregulation may result in altered glutamatergic signaling that could contribute to depression. Here we aim to determine if increased EAAT3 expression, the neuronal glutamate transporter, could reduce susceptibility to depression due to unpredictable chronic mild stress (UCMS), a well validated model of stress-induced depression. Mice with EAAT3 overexpression driven by CaMKIIα-promoter (EAAT3^{glo}/CMKII) and the control group (EAAT3^{glo}) were used to assess anxiety and depressive-like behaviors. In baseline conditions, EAAT3^{glo}/CMKII mice showed anxiety-like behavior in Open Field Test and lower despair behavior in Tail Suspension Test. However, UCMS did not increase immobility time or trigger anhedonia in EAAT3^{glo}/CMKII mice. Furthermore, WT mice challenged to UCMS showed upregulation of EAAT1 expression levels, NR2A and NR2B subunits NMDA receptor, and GluR1 subunit AMPA receptor protein levels in the hippocampus. Our results indicate that dysregulation of glutamatergic components in the limbic-cortical areas in the brain is related to depressive-like behaviors. Moreover, we suggest that EAAT3 overexpression in the forebrain in mice could be related to a resilient phenotype to chronic stress.

Astroglial glutamate and D-serine released via Cx43 hemichannels during training regulate NMDAR-dependent transmission and short-term fear memory in the basolateral amygdala

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Recent studies suggest that astrocytes release neuroactive substances known as gliotransmitters into neighbouring synapses, which modulate synaptic plasticity. The connexin 43 hemichannel (Cx43HC) is one of the main mechanisms responsible for their release and its blockade in the basolateral amygdala (BLA) has been shown to impair cued fear memory consolidation. Here we report an increase in Cx43 hemichannel activity in astrocytes from the BLA that could be observed 1 h but not 3 h post training for cued fear memory. The selective blockade of Cx43HCs via microinfusion of the TAT-Cx43L2 peptide into the BLA before training induced amnesia for auditory fear conditioning as assessed 24 h after training, without affecting learning. The microinfusion of TAT-Cx43L2 together with individual putative gliotransmitters glutamate, D-serine, glycine, ATP and glutamine was unable to prevent the amnesic effects of Cx43HC blockade. Only microinfusion of a combination of glutamate and D-serine prevented the amnesic effect of TAT-Cx43L2, suggesting a role for NMDA receptors (NMDAR). When BLA slices were recorded for NMDAR activity, incubation with TAT-Cx43L2 decreased NMDAR-mediated currents, effect that was prevented by incubation with glutamate and D-serine. TAT-Cx43L2 decreased NMDAR activity in brain slices containing astrocytes but had no effects on the responses to NMDA in primary cortical neurons, ruling out a direct action of the peptide on neuronal NMDARs. Intra-BLA micro-injection of TAT-Cx43L2 before training caused memory disruption as assessed 1 h after training, which again could be prevented by glutamate and D-serine, but had no effect on learning. However, the microinfusion of TAT-Cx43L2 into the BLA after training had no effects on memory 1-hour post training. The present results suggest that Cx43 HCs mediate the release of glutamate and D-serine from astrocytes, which are necessary and sufficient to activate NMDAR at postsynaptic neurons specifically during training, allowing the formation of short-term and subsequent long-term memory, but have no role on learning *per se*.

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Pannexin 1 dysfunction in the retina during natural ageing

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Ageing is a chronic degenerative process caused by multifactorial phenomena accumulated during life course. In the visual system, ageing is linked to a decline of functional activity, visual acuity, lowering contrast sensitivity and impaired dark adaptation. In the retina, there is decreased cell numbers of retinal ganglion cells (RGC) and photoreceptors, degeneration of the optic nerve, detritus accumulation, oxidative stress and chronic inflammation.

So far, Pannexin 1 (Panx1) channels have being related to the beginning and progression of several inflammatory conditions associated with ageing such as Alzheimer's disease, Parkinson, glaucoma, age-related macular degeneration and ischemia. Opening of Panx1 channels can be induced by several neurotoxic conditions such as ischemia, mechanical stress, activation of purinergic and NMDA receptors, high potassium and amyloid peptide. Under such conditions, ATP released through Panx1 channels can induced cytotoxicity through activation of purinergic receptors and additional Panx1 activation, leading to a sustained increase of intracellular Ca^{2+}, membrane depolarization, caspase/inflammasome activation and eventually, neuronal death. Although Panx1 is widely expressed along neuronal retinal cells, it is unknown how Panx1 activation contributes to the disruption of neuronal network during ageing.

For this purpose, we evaluated Panx1 levels together with inflammation markers expression (GFAP, microglia CD11b and neuronal death FJADE) in mouse retina at different ages through western blot and immunofluorescence microscopy respectively. To evaluate functional activity of Panx1 channels, dye uptake assays in the presence of Panx1 inhibitors in retina explants were made. Finally, an electrophysiology approach through 252 multielectrode array (MEA) in the presence of Panx1 inhibitor was used to evaluate RGC function in different luminous stimulus.

Interestingly, increased levels of Panx1 proteins and inflammation markers were detected in aged retinas (5-14 month old) compared to younger animals (1-2 month old). Consistently, aged retinas also presented higher dye uptake respect to younger retinas, suggesting an increase activity of Panx1 channels. In addition, during MEA recordings, we detected hyperactivity of RGC during photopic stimulation, which was reduced by Panx1 inhibitor Probenecid. On the contrary, our mouse line lacking Panx1 gene did not showed degenerative sings in aged retinas. Altogether, this data strongly suggest that Panx1 dysfunction in aged retinas could be contributing to inflammation and consequent changes in neuronal excitability and cell death.

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Morphological and geometrical analysis of the somatodendritic domain and receptive space of individual ventral tegmental area and substantia nigra pars compacta dopaminergic neurons in the mouse

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Ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) dopaminergic neurons play important roles in motivation, preference and habit formation, and motor control. Respectively part of meso-cortico-limbic and nigro-striatal systems, neurons of these regions have been historically differentiated by their relative involvement in limbic (VTA) vs motor (SN) functions. At the same time, similarities in electrophysiological, anatomical and functional characteristics have also been described. To explore whether structural features of neurons underlie differences or similarities between the two groups, a comparative analysis of the size, shape, orientation, dendritic tree complexity and receptive space of individual neurons was carried out. For that, in vivo juxtacellular labeling, high resolution confocal microscopy acquisition and vector-based reconstruction of the complete somatodendritic domain (SD) of 13 VTA and 12 SNc dopaminergic neurons was carried out. Both populations exhibited large within-group variation in SD size and dendritic tree complexity. When considering their location, however, ventral VTA neurons exhibited smaller and simpler SD than dorsal VTA or SNc neurons. Regarding orientation of the SD, VTA neurons as a group exhibited a dorso-medial / ventro-lateral preference, contrasting the bias towards the dorso-lateral quadrant shown by SNc neurons. SD extension of individual neurons appeared noticeably larger in relation to the size of VTA and substantia nigra (SN) regions, with individual neurons stretching on average ~50%, ~40% and ~30% of the medio-lateral, dorso-ventral and antero-posterior extension, respectively, of VTA or SN. Not surprisingly, dendritic trees cross-over across VTA and SN subnuclei but also between VTA and SN regions. Finally, VTA and SNc neurons showed similar convex hull volumes, a proxy for individual neurons' receptive space (RS, in turn a 3D analogous of a neuron's receptive field). Interestingly however, when simulating how much of the individual neurons' RS would overlap with other adjacently located neurons as a function of distance in a common anatomical space, VTA neurons' RS overlapped significantly more with each other than did SN neurons' RS. This difference, which suggests the potential for VTA neurons to "share" more of their afferents than SN neurons, is likely due to the more "rounded" shape of VTA neurons' RS. The results are discussed in light of the proposed existence of VTA functional subpopulations, the developmental constraints underlying dendritic orientation, and the possible differences in integrative properties in relation to receptive space geometry and size.

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ORAL COMUNICATIONS II

Effects of postural control on the upper limb during a pointing task with online correction

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Introduction: During our daily life activities it is common to perform a voluntary task while we maintain the bipedal posture. We are continually making online corrections when we make a reaching, especially if the target moves once the motor act is started.

Methodology: 19 young subjects performed a reaching(pointing) task with online correction in different situations of postural instability(firm bipedal, bipedal on foam and unipedal on foam). Target positions changes could occur at 200, 400 or 600 ms. after the movement onset. The variables analyzed were: movement times, precision and efficiency (time and precision) of the pointing.

Results: No significant differences were observed between the different postural conditions in the variables studied. However, the participants showed significant differences in movement times, error and efficiency when the target disturbance was done at 600 ms. (shorter correction time) compared to 200 and 400 ms disturbances.

Conclusion: These results show that postural instability conditions do not alter the efficiency of reaching control mechanisms. This suggests a relevant role of the vestibular system plus the visual system for postural adjustments during reaching in situations of instability. Additionally, these results suggest that the feedback mechanism is essential to complement the other reaching mechanisms (feedforward and anticipatory internal models) in a task that requires online correction.

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Working memory load-related theta power decreases en frontal cortex: intracortical evidence

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(Sponsored by Fondecyt)

Working Memory (WM) is a fundamental cognitive skill that guides our goal-directed behavior. This hierarchical process links sensory representations to specific responses, through intermediate representations relevant to the task and action plans. A distributed network of brain areas participates in this process, exhibiting sustained activity during the period of maintenance in the absence of sensory stimuli. This sustained activity is generated by reverberant discharges in an interconnected prefrontal cortex (PFC) network, and between the PFC and other brain areas, such as the posterior parietal lobe, the inferior temporal cortex, and subcortical structures. PFC activity is involved not only in the storage of information but also in a control process that sustains reverberant activity and eventually manipulates WM information. Electrophysiological (EEG) studies have revealed the crucial participation of oscillatory activity in theta (4-8 Hz), alpha (8-12 Hz), and gamma (30-100 Hz) bands in WM, however, intracranial recordings yield mixed results, depending on the brain area being recorded from. During the maintenance stage, memory load increases theta activity, and related medial frontal theta activity controls processes and successful memory storage. We recorded intracranial EEG with depth electrodes in 17 patients (12 female and 7 male; median age 30.5 years) with refractory epilepsy who were performing a Sternberg WM task. Participants first watched a memory set of two, four, or six consonants that had to be memorized and, after a black screen that was shown for three seconds, a target stimulus was displayed. We evaluated patterns of theta power changes as a function of memory load during maintenance. The subjects showed an decrease of theta activity in frontal during maintenance and this decrease was proportional to memory load. In contrast, theta frequency power in the parietal region increased during maintenance modulated for memory load. This result suggests that theta power changes serve different cognitive functions in different brain areas. Thus, brain oscillations studied through direct intracranial recordings could be useful to better differentiate the distinct contributions of different areas to WM.

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Lempel-Ziv complexity of the EEG signal strongly and non-linearly predicts performance under propofol sedation

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General states of consciousness (GSC), like wakefulness, dreamless sleep or anesthesia, strongly delineate the cognitive processes and possible experience one can have. Neural signatures that could distinguish between GSC would be of immense use for clinical purposes but also in elucidating the neural basis of conscious experiences and cognition. Several such attempts have been made using ERPs, spectral and connectivity-based metrics, however because a low and sometimes circumstantial correlation with GSC, they have not yielded a robust and general index of GSC. Influential theories of consciousness have started to put importance on other ways to quantify and characterize brain activity: entropy-related measures. Here we show that the Lempel-Ziv complexity (LZc) of the EEG signal during propofol sedation strongly distinguishes (Cohens d =1.7) subjects according to their responsiveness to a simple auditory discrimination task. We show that this effect is consistent across practically all subjects analyzed and that LZc has a non-trivial topological distribution. We also observed that LZc was not directly dependent on any specific frequency band, as shown by its invariance to previously notch-filtering the EEG signal. Thus, brain activity complexity appears as a promising candidate for distinguishing between GSC induced by anesthesia. Also our results show that brain complexity cannot be explained easily by spectral changes, thus putting forward the notion that it is a somewhat orthogonal dimension of brain activity analysis.

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Spontaneous brain dynamics characterization in Parkinson's Disease

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Idiopathic Parkinson's disease (PD) is a chronic neurodegenerative disease characterised by motor and cognitive impairments, resulting from the loss of dopamine producing neurons. It has been shown that PD is characterised by a loss of segregation at brain network level [Kim et al., 2017]. In other hand, some of patient motor and cognitive functionality can be restored following sensory-motor synchrony training [Dalla Bella et al., 2017]. This work aims at relating the suggested connectivity changes in PD to dynamical fluctuations at rest. The spontaneous EEG displays a repertoire of quasi-stable spatiotemporal patterns that reflect the underlying networks dynamics that could be related to cognitive functions. These patterns or brain states and their transitions over time can reflect fundamental computational properties of the brain, shaping human behaviour and brain function. Here, we applied Hidden semi-Markov models (HsMM) [Trujillo-Barreto et al., 2019] to investigate the switching dynamics of the EEG in PD, before and after an auditory-motor synchronization training (AMST). RS-EEG closed-eyes (8min) was recorded from PD patients (PD=15) and healthy controls (HC=15) in 2 sessions. PD sessions preceded and followed AMST. Data was cleaned (filter 4-30Hz and ICA based artifact rejection). Data envelope was obtained by Hilbert Transform. PCA was used for dimension reduction. We use HsMM with MVN distribution as shared emission model between groups and log normal as duration model. We define an optimal number of states based on the best likelihood separation between groups. The Variational Bayes framework is used to infer parameters of transition (T), duration (D) and emission (E) models. The most probable state sequence (S) is derived from model. Metrics as state occupancies (FO) and mean-life time (MLT) are computed from S. We compared models and metrics between participants and groups and relate them to behavior data. The T and D models differed between groups, leading different FO and fewer T in PD. Following AMST, metrics result closest to the HC group. PD-D shows distribution similarities to the HC-D after AMST. Specific patterns of EEG state dynamics distinguish between PD and HC. We argue that these differences may reflect altered changes in connectivity. We show the capabilities and limitations of the model to identify patterns in altered dynamics. Future work should relate such patterns to cognitive function, both to serve as markers of disease and disease progression, and as a framework for understanding the relationship between brain activation and cognition.This study contributes to our knowledge about the brain mechanisms underlying PD.

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The ascending neuromodulator system role on meso-scale network integration

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Decades of cortico-centric focus in neuroscience have led to a theoretical dissociation between the central and autonomic nervous systems. Despite this conceptual schism, there is now ample evidence that the autonomic nervous system provides important constraints over ongoing cognitive function. Although a connection between the autonomic nervous system and attention has long been hypothesized, there is currently a lack of direct empirical evidence for how their interaction manifests in the brain. Here, we examine the role of ascending arousal, mental effort and attentional load on the large-scale network dynamics by combining pupillometry, functional MRI and graph theoretical analysis to analyze data from a visual motion-tracking task with a parametric load manipulation. We found that attentional load effects were observable in measures of pupil diameter and in a set of brain regions that parametrically modulated its BOLD activity and meso-scale network-level integration. In addition, we identified a network involved in mental effort that increased its activity and integration with attentional load, a result that was mirrored by alterations in pupillometry. Our results provide confirmatory evidence for the adaptive gain theory and strengthen the relationship between ascending noradrenergic tone, large-scale network integration and cognitive task performance.

High-order interactions among brain areas show higher redundancy with aging

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Understanding the functional interactions between different areas is fundamental to explain a set of phenomena related to aging that manifest at the level of correlations. Several researchers in lifespan studies have proposed that changes in brain functional connectivity (FC) can explain certain aspects of aging. In particular, it has been shown that the FC decreases along lifespan mostly in anterior and posterior areas (Demoisseaux2007), and the modularity/segregation also decreases (Chan2014). These studies among others represent the most common approach to these problems and are focused on pairwise correlations. However, the brain is a complex structure and high order interactions are expected. This more general approach allows that concepts as synergy and redundancy arise in the context of brain interactions. A pioneering study that uses multivariate information theory to analyze interactions of third order in resting-state fMRI data along lifespan is Borja2018. The authors use the Interaction Information measure to identify synergistic or redundant interaction among triplets of brain regions (Diez2015). They found that an important role is played by the redundancy in the Default Mode Network. Following this idea, we generalize this study to high-order interactions among brain areas using the concept of O-Information (Rosas2019). The O-information generalizes the concept of Interaction Information and afford to characterize interactions of n-tuples with $n \geq 3$ and classified them as redundant or synergistic. We analyze the fMRI resting-state data presented in Borja2018 (164 patients ranging from 10 to 80 years). We show that there are high order interactions among brain areas and they change along the lifespan. Our results show an increase in the redundancy and decrease in the synergy as the order interactions are increased. Moreover, we found an increase in the prevalence of redundancy and a decrease in the prevalence of synergy along the lifespan. The subjects ranging in age from 60 to 80 years shows statistically significant differences compared to other younger groups of patients.

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The structural core for cortical ignition is preserved in the connectome of mammals

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One way to study the fluctuations of brain activity is the transition from low to high firing rate on cortical areas, which is called ignition. The capability of cortical regions to flexibly sustain an “ignited” state of activity has been discussed in relation to conscious perception or hierarchical information processing. In previous modelling work, we showed that the intrinsic propensity of cortical regions to get ignited is related to the topological core of human connectome. Now, using the connectomes of different mammals, we assessed if the relationship between ignition and anatomical cortical core is preserved. We simulated the resting-state dynamics of the cortical activity using mean-field whole-brain models and evaluated how dynamic multi-stability and ignition relates to their anatomical organization using network analysis. We found that the level of global excitation required to first trigger ignition is substantially smaller for the model when using either the macaque, rat, mouse or cat connectomes. Furthermore, the number of ignited nodes increases with the level of global excitation, being the newly recruited nodes those that belong to the innermost shells of the core. The ignition outside the initial core is more gradual than for randomized networks and correlates better with the s-coreness than with any other metrics, such as the degree or strength. We conclude that the relationship between the core structure and the ignition is preserved in the analyzed mammals. Because the number of connectomes is low, considering the mammal’s diversity, this seminal work encourages the use of richer datasets to confirm this outcome. We speculate that this structural core, conserved in mammals, supports a boosted ignition dynamic.

Dorsomedial prefrontal cortex participates in the modulation of the uncertainty independent of the learning rate

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The prefrontal areas codify the value in the decision making and the update of the value of the options occurs mainly during the feedback, in this context, a high uncertainty is related to a decrease in the learning speed (Diederen, Spencer, Vestergaard, Fletcher & Schultz. 2016). Another way of assessing uncertainty is the condition of volatility which, unlike uncertainty, is associated with an increase in the rate of learning (Massi, Donahue & Lee. 2018). It is known that as the learning rate increases, uncertainty decreases; however, there is no clarity of the brain areas that census uncertainty. Our study analyzes a decision-making task where subjects must predict under two conditions: Uncertainty and Volatility. Our hypothesize that uncertainty coding occurs in prefrontal areas typically related to value. 30 healthy subjects, between18 and 35 ages, resolved a decision-making task under fMRI in two conditions: Uncertainty and Volatility. The BOLD signal response was analyzed separate regressions for each task condition during the feedback period. Behavioral model was designed in order to evaluate the learning rate of each condition of the task. This model adjusted the prediction of each trail based in the prediction error. The Behavioral analysis showed that subjects learned less in the uncertainty condition (alpha= -0.0813, p value=0.0210), while in the volatility condition the learning rate increased (alpha= 0.1531, p value=0.0210). The neurobiological activity during feedback in high uncertainty condition demonstrated activation on prefrontal areas typically related to value coding as orbitomedial prefrontal cortex and dorsomedial prefrontal cortex, and for the low uncertainty condition, an activation of ventromedial prefrontal cortex was observed during feedback. The condition of volatility during feedback showed an activation of dorsomedial prefrontal cortex and striatum. Additionally we analyzed the coincident areas for conditions of high uncertainty and volatility during feedback period, the results demonstrate overlapping areas in the dorsomedial prefrontal cortex. In conclusion, Our behavioral results demonstrate a higher learning rate in the volatility condition compared with high uncertainty, however it is possible observed a coincident activation in the dorsomedial prefrontal cortex for both conditions during feedback independent of the learning rate.

FONDECYT regular 1181295. Modulación del control cognitivo proactivo a través del entrenamiento oscilatorio prefrontal (P. Billeke)

POSTER SESSION I

1) The response of XBP1 under the stress produced by EGFR-Ras expression in glioma-like *Drosophila* model

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Genetic lesions in human brain tumors and glia cell neoplasm, as the glioblastomas, harbor mutant forms of the epidermal growth factor receptor (EGFR) and phosphatidylinositol-3 kinase (PI3K) associated with a constitutive kinase activity that chronically stimulates Ras signaling to promote cell proliferation and migration. The harsh environment of a tumor induces a stress in the endoplasmic reticulum (ER) that drives the unfolded protein response (UPR) mediated by Inositol Requiring Enzyme 1 (IRE1), a transmembrane protein that resides in the ER acting as sensor stress in this organelle. IRE1 splices the mRNA of the X-box binding protein (XBP1) through its RNAse domain and generates an active isoform of this transcription factor that regulates the expression of genes for protein production and lipid biosynthesis contributing to the uncontrolled growth of the tumor. During the last decade, the fruit fly *Drosophila melanogaster* has become an important model system for cancer studies, since many molecular pathways involved in tumorigenesis and metastasis are conserved among flies and humans. The overexpression of the constitutive co-activation EGFR or Ras in the glial cells of *Drosophila* produces an increase in proliferation, excessive migration and the invasive neoplasia of the glial cells. In this context, we set up the glioma-like model in *Drosophila* larvae by the overexpression of a constitutively activated EGFR variant (EGFRλ mutant) and Ras (Ras85DV12 mutant) in glia, using a repo-Gal4 glial-specific driver and GFP as a tracker. Then, we performed qPCR and immunostaining assays in order to evaluate the response of XBP1 splicing and ER proteins in glial cells as a measure of UPR activation. Glial-specific activation of the EGFR-Ras pathway alone, through overexpression of EGFRλ or Ras85DV12, induced excess glia in the larval brain and later pupal lethality. Additionally, our results in qPCR and immunostaining assays suggest that is necessary to expand and deepen the study in order to evaluate the effect of EGFR-Ras expression on other UPR pathways associated with XBP1.

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2) Study of new phenethylamine derivatives as controller in *Drosophila melanogaster* oviposition. Toward a better description of monoaminergic system in invertebrates

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The monoaminergic system (SM) is crucial in development, survival and reproduction of various insects. The biogenic amines: Dopamine (DA), Serotonin (5-HT), Octopamine (OA) and Tiramine (TA), whose extracellular concentrations are regulated by specific transporters (DAT, SERT and OAT), has significant functions in the mentioned behaviors.
In our group we are carrying out experimental and computational studies in order to generate insights to describe the monoaminergic system in *Drosophila melanogaster* as a model insect in the oviposition process. The structural information of monoaminergic transporters has been used for the design of new compounds interacting with monoamine transporters, specifically with DAT. Thus, two new compounds, β-fluor-phenylethylamine and ρ-chloro-β-fluor-phenylethylamine, were studied using docking and molecular dynamic simulations. The complexes DAT/Ligand showed promising free energy values (-5.36 and -6.01 kcal/mol respectively). Subsequently, using conventional molecular dynamics during 1.5 μs and MM-PBSA calculations the protein-ligand free energies were obtained. Our findings show similar free energy values both compounds and respect to the substrate DA. Once the computational study was done, *in vivo* studies to evaluate the effect of these compounds on the oviposition process in *Drosophila melanogaster* were carried out. Both molecules were evaluated in 4 different fly strains (W1118, CS, Tβh and DAT6) showing a negative impact on the oviposition. Finally, our findings describe two new potential inhibitors of monoamine re-uptake in *Drosophila melanogaster* as regulator of reproduction which can be used to control pest invertebrates.

3) A hydrogen bond network as responsible in the biological activity differences of two new β-benzyloxy-β-phenetylamine derivatives in SERT

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The human serotonin transporter (hSERT) is one of the macromolecules responsible of regulating the concentrations of the neurotransmitter serotonin at the synaptic cleft. Therare some antidepressants that act as selective inhibitors of hSERT like Fluoxetine, Citalopram and Sertraline. In our recent studies, new β-benzyloxy-β-phenetylamine derivatives have been evaluated as potential antidepressants. Two of them, SME and SDM which are methylated and demethylated derivatives respectively, shows high biological activity on hSERT but a difference in one order of magnitude (higher SMD) was observed.

In order to rationalize the experimental differences and to determine structural differences astudy using molecular modeling was done. Here, SDM and SME were evaluated at the central binding site of hSERT and using molecular dynamics simulations the main interactions were studied.

A Wild-Type version of hSERT, using the crystallized version of it obtained from Protein Data Bank (PDB ID : 5I6Z), was done. Afterward, a molecular docking and molecular dynamic simulations during 1 microsecond were carried out. Our findings show that SME generates a hydrogen bond network, which hinders the protein from stabilizing as a whole.

On the other hand, SDM does not keep any hydrogen-bond during the simulation, but more van der Waals interactions than SME were observed. The latter makes the protein more stable as a whole, which explains why that ligand has a higher biology activity.

4) Design, synthesis and biological evaluation of new β-benzyloxyphenetylamine derivatives as monoamine transporter inhibitors

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Background: Serotonin transporter (SERT) is a member of the neurotransmitter sodium symporter family of transporters and represents an important biological target for antidepressants, but also for illicit drugs such as cocaine and MDMA. β-alkoxy-β-phenethylamine derivatives have been tested on several monoamine receptors and MAO without further success. Since these molecules share structure similarity with commercial SSRIs, the purpose of this study is to find out if the modifications on the phenethylamine core, mainly in β position and amine group could provide activity as blockers of SERT. Methodology: Based on the Structure-Activity relationships of commercially available SSRIs, we synthetized a new series of β-Benzyloxyphenetylamine derivatives using a copper-catalyzed aminooxygenation or aziridination of styrenes as the key step in the synthesis route. To test their uptake inhibition activity on hSERT-expressing HEK cells, we employed a high-throughput fluorescence assay based on IDT307 (APP+) as a fluorescent substrate. In addition, we performed calcium efflux assays in cells co-expressing monoamine transporters and calcium channels to study the interaction of the β-benzyloxyphenetylamine derivatives with SERT and hDAT. Finally, computational studies were performed to determine how these compounds interact at the ortosteric binding site of the SERT. Results: 32 new β-Benzyloxyphenetylamine derivatives were obtained using both strategies of synthesis, which the copper-catalyzed aziridination of styrenes was the most effective route of preparation of these compounds. Experiments with APP+ showed that *para* substitution in the benzyloxy ring and the dimethylamino group are important for SERT inhibition. On the other hand, the monoamine transporter coupled to calcium channel assay not only confirmed their pharmacological mechanism of action as blockers, but also displayed selectivity for hSERT compared to hDAT. Finally, the molecular docking experiments suggests that the β-benzyloxyphenetylamine compounds bind at the central site of SERT in agreement to the recent X-ray data. Conclusions/Remarks: Our results showed that these new substituted β-Benzyloxyphenetylamine derivatives act as inhibitors of the SERT and provides valuable information for development of new SSRIs. Keywords: Serotonin Transporter, Substituted Phenethylamines, Serotonin Transporter Inhibitors

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5) Tyramine crossing Dopamine transporter. A Steered Molecular Dynamic study

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Tyramine as octopamine and phenethylamine are part of the trace amines in vertebrates, however a major role of these monoamines has been described in invertebrates. Tyramine is the synthetic precursors of octopamine, but at the central nervous system level tyramine has an independent role. In a general sequence, once the neurotransmitters are released to the synaptic cleft a re-uptake process by a specific transporter occur. For tyramine and octopamine in *Drosophila melanogaster* no a specific macromolecule in charge of these function, it has not been reported.

Based on the structural similarities with dopamine and in order to evaluate the participation of Dopamine Transporter (DAT) as target in the tyramine re-uptake a non-equilibrium methodology was used.

Here, using steered molecular dynamic (SMD) simulations a force profile was generated. This methodology allows us to evaluate the more important interactions when the ligand is crossing the transporter from the extra- to intracellular space. The molecular interactions are traduced as a force peak. Thus, in two different positions inside the transporter were selected the more representative interactions (higher force values) and molecular dynamic simulations during 1 microsecond were carried out. Our results, shown interaction forces between 900 and 1000 pN associated with molecular interactions of the ammonium group and the aromatic centre of DAT. In addition, comparative studies of electrostatic potential were carried out in order to identify similarities and differences of protein/ligand complex during the simulation.

6) I*n-silico* studies of new 2-benzyloxitryptamine derivatives as human serotonin transporter blockers

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Human serotonin transporter (hSERT) is the protein responsible for the serotonin (5-HT) reuptake from the synaptic cleft. Selective serotonin reuptake inhibitors (SSRI) have been widely used to increase the concentration of 5-HT in the synaptic cleft. However, both side effects such as no-selectivity of these drugs require new design strategies to contribute at the control of major depressive disorders (MDD). In this work, using molecular modeling methodologies new potential drugs acting as SSRIs, 2-benzyloxitryptamine derivatives (2BTD) have been proposed. Our design involves studies using Escitalopram and Fluoxetine among others compounds in order to describe the structural requirements of new SERT-ligands. Our resultsshow the main interactions of (2BTD) into the binding cavity of hSERT and, in comparison with known inhibitors, we observed an important interaction conservation. In addition, molecular dynamic simulation studies during 400 ns were carried out in order to generate structural insights. A well-defined role of D98, Y95 and aromatic centers to accommodate 2BTDs into the cavity of SERT was observed.

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7) Role of dopamine transporter as target of octopamine and tyramine in *Drosophila melanogaster*. A study from *in vivo* to *in silico*

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A monoaminergic system(MS) of fundamental importance in invertebrates is the *octopaminergic system*, which regulates different central and peripheral processes. Octopamine (OA) and its biosynthetic precursor Tyramine (TA), are endogenous monoamines linked to important biological processes in insects as and has been associated with learning and memory, as well as with the feeding behavior. At same as MS in mammals, it is mainly constituted by the neurotransmitter, their receptors, their associated metabolic enzymes and transporters that reuptake the neurotransmitters. The molecular entities responsible for octopamine availability, the octopamine transporter (OAT), has not been identified in certain insect species. For instance, no OAT has been reported in the fly *Drosophila melanogaster* (Dm), but it has been described for other insects. Although OA and TA have been related with the oviposition process the specific role of each monoamine remains unclear. Thus, based on the structural similarities of OA and dopamine we evaluate the dopamine transporter (DAT) as biological target of OA and/or TA through *in vivo*, *in vitro* and *in silico* evaluations. Our result shows a complementary role or TA/OA on the oviposition process. On the other hand, although *in vitro* and *in silico* results indicates a specific interaction with DAT, the ligands would not be transported by the transporter. These studies provide new information that contributes to our understanding of amine availability in insects and could encourage the development of future generations of molecules for selective control of pests.

Fondecyt 1161375

8) Therapeutic effects of nicotine in specific Parkinsonian genetic backgrounds using a *Drosophila* model

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Synphilin-1 is a protein that interacts with a-Synuclein, it is known that both proteins have a role in the development of the pathology of Parkinsons disease and the formation of Lewy bodies. Parkinson´s disease has no cure. However, it has been observed that there is a clear correlation between tobacco consumption and a lower incidence of Parkinsons disease onset. Nicotine, an acetylcholine agonist, is a substance found in common tobacco (*Nicotiana tabacum*). Nicotine is the principal chemical compound that causes tobacco addiction. *In vivo* and *in vitro* studies have shown that there is a beneficial effect of nicotine in sporadic and genetic models of the disease. In this work we evaluate the protective effect of nicotine against the expression of Synphilin-1 and α-Synuclein in *Drosophila melanogaster* dopaminergic neurons. Our results indicate that, in our fly model, nicotine has a protective effect on survival, motility and maintenance of dopamine levels, but not on dopaminergic neuron survival. This suggests that nicotine treatment helps maintain metabolic function in the surviving dopaminergic neurons that express Synphilin-1 and α-Synuclein, making nicotine an interesting therapeutic seed drug for the understanding of phenotypic modulators of the disease and the development of new treatments.

9) Dysbiosis induces changes only in locomotor parameters in flies

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Monoamines like serotonin (5-HT) and dopamine (DA) are crucial modulators of the activity of several central nervous system (CNS) processes. For instance, 5-HT has been associated to anxiety, sleep behavior and mood regulation, while DA is a catecholamine involved in motor control and hedonic behavior. Interestingly, these monoamines can be also found in the gut and throughout the entire body, mainly in the circulation. Actually, recent evidences support the idea that in the regulation of peripheral amine levels, the gut (and the community of bacteria living there) plays an important role. In this work we generated a *Drosophila* model for gut dysbiosis (microbial imbalance) by feeding flies one antibiotic (kanamycin, 0,5mM concentration, 14 days). By using a setup we previously described (Buridantracker; Molina-Mateo et al., 2017), we evaluated in single male flies several motor and non-motor behavioral parameters in the kanamycin-treated flies. We also used high performance liquid chromatography (HPLC) to measure eventual changes in brain amine levels (DA and 5-HT) after this treatment. The results obtained show that the kanamycin treatment induces changes in motor parameters in flies like speed and distance traveled, while non-motor parameters including olfactory responses to an aversive odorant and centrophobism are not modified. The kanamycin treatment seems not to be associated to variations in biogenic amines in fly brain. It is necessary to evaluate the effect of the treatment on the gut microbiota in order to better understand how the kanamycin-induced dysbiosis is responsible for the specific changes in locomotor parameters.

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10) Role of the serotonergic system in pre-symptomatic phase in a Drosophila model of Parkinson's Disease

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Parkinson's Disease (PD) is a neurodegenerative disease characterized by motor and non-motor symptoms (MS and NMS, respectively). Although PD is typically described by a progressive loss of a specific group of dopaminergic neurons, there are other neural systems affected including the serotonergic system. In PD patients, abnormalities in the serotonergic system have been associated with NMS at pre-symptomatic and symptomatic stages of the disease, and more recently with MS as well. Nevertheless, little is known on how the serotonergic system contributes to the onset of MS or how it is involved in pre-symptomatic stages of the disease. In this work, we used a *Drosophila* model of PD generated by a deletion of the *PINK1* gene (from now on PINK1^{B9}). PINK1 is a kinase protein with functions associated to mitochondrial quality control. These mutants exhibit a pre-symptomatic phase with olfactory impairment and a symptomatic phase with locomotor defects. Here, we characterized the serotonergic system in PINK1^{B9} flies. During the pre-symptomatic phase, lower 5-HT content was detected in brains of young PINK1^{B9} flies, which is consistent with a lower activity of the serotonin transporter (SERT). To increase the serotonergic signaling in young PINK1^{B9} flies before the onset of locomotor defects, we fed flies with fluoxetine, a selective SERT blocker. This treatment partially prevented the locomotor defects observed in old PINK1^{B9} flies, but it negatively affects the locomotion in older w^{1118} control flies. Thus, we propose that a possible dysfunction in the serotonergic system during the pre-symptomatic phase could contribute to the parkinsonian phenotype in older PINK1^{B9} flies.

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11) Evaluation of compulsive behaviors in EAAT3glo / CMKII mice

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Evaluation of compulsive behaviors in EAAT3glo / CMKII mice Macarena Churruca, J. Patricio Casanova and Pablo R. Moya. Programa de Magíster en Neurociencias, Universidad de Valparaíso. Introduction: Obsessive Compulsive Disorder (OCD) is a disabling neuropsychiatric disease and, in about 50% of cases, resistant to traditional pharmacotherapy using drugs targeting serotonin neurotransmission. Therefore, it is relevant to model the disease using animal models to simulate compulsive behaviors, in order to investigate the mechanisms underlying this pathology and to potentially find novel and more effective pharmacological treatments. In our laboratory we study the glutamatergic hypothesis of OCD and developed the EAAT3glo/CMKII mouse that overexpresses the neuronal glutamate transporter EAAT3. This mouse model has recently been validated, exhibiting increased compulsive baseline behavior (grooming, marble burying) as well as increased anxiety. Aim: To evaluate compulsive behaviors of EAAT3glo / CMKII mice in other paradigms that have not been measured, such as operant conditioning and extinction, nesting behavior and excessive plastic chewing. Methods: Using ROBucket boxes (Devarakonda et. al 2016) built in our laboratory and tested in a pilot group (n = 3), the observed operating behavior fulfills the 3:1 criteria for three consecutive days for 9 days. The evaluation of EAAT3glo control mice (n = 8) and an EAAt3glo / CMII mice (n = 8) is currently ongoing in an operant conditioning test with food restriction (85% of initial weight) followed by an extinction protocol. In addition, nesting and plastic chewing behaviors are tested in same groups. Results: EAAT3glo / CMKII mice are expected to exhibit increased compulsive behavior compared to control mice, and also impairments in extinguishing acquired operant behavior. Conclusions: We expect this study would strengthen our animal model at the behavioral level as a valid model of OCD, offering new routes for the development of possible pharmacological treatments. Keywords: OCD, EAAT3glo / CMKII, ROBucket, Operant Conditioning and Glutamate.

12) Selective deletion of CB1 receptor from serotoninergic neurons modulates anxious behavior in mice

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(Sponsored by To Eric Delpire, PhD, Laboratory For Providing Us With The Conditional CB1flox/flox Mouse.)

Serotonin (5-HT) is involved in the control of emotional responses and impairment of 5-HT neurotransmission has been classically linked to the pathophysiology of mood and anxiety disorders. The endocannabinoid (eCB) system participates in a wide range of brain functions including emotional processing and anxiety. While manipulations of eCB system are known to control 5-HT levels in different brain areas, including the amygdala, hippocampus and prefrontal cortex (PFC), their relevance to the pathophysiology of mood and anxiety disorders remains unclear. Here, we examined the behavioral effect on the selective knockout of type 1 cannabinoid receptor (CB1R) in serotonergic (5-HTergic) neurons using the open field test (OFT), the elevated plus maze (EPM) and the dark light test (L/D). Selective CB1R knockdown in 5-HTergic neurons (Pet1*CB1-/-* mouse) was obtained by crossing the Pet1-Cre mouse (5-HT driver line) and the CB1 *flox/flox* mouse. CB1*flox/flox* mouse (lacking Cre) was always used as a control. We first confirmed with polymerase chain reaction (PCR) and immunohisto-fluorescence (IF) the deletion of CB1Rs at 5-HTergic neurons in Pet1CB1-/- mice. In genotyping PCR, bands corresponding to the lox-p sequence and the Cre recombinase sequence were both present in DNA electrophoresis gels, whereas IF in brain sections shows the absence of CB1R expression in both the soma of 5-HTergic neurons at the raphe nucleus and their terminals in the cortex, hippocampus and basolateral amygdala. In the OFT, Pet1*CB1-/-* mice spent less time in the center of the arena and entered the center less frequently, without displaying significant differences in the locomotor activity compared to control animals. In addition, we found a significant decrease in both the time spent in the open arms and in the frequency of entry to the open arms in the Pet1*CB1 -/-* mouse when tested in the EPM. Further, in the L/D test, we found that the Pet1*CB1-/-* mice display a significant decrease in the time, frequency of entries and the distance traveled on the bright side. Altogether, our findings reveal that the selective deletion of CB1Rs at 5-HTergic neurons and terminals increases anxious behaviors likely by increasing the level of 5-HT in brain areas such as the basolateral amygdala, PFC and hippocampus. Importantly, our work highlights the relevance of eCB and 5-HT interactions in the pathophysiology of anxiety disorders. Acknowledgements to Eric Delpire, PhD, Laboratory for providing us with the conditional CB1*flox/flox* mouse.

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13) Evaluation of the Serotonin Transporter as a moderator of the effect of Voluntary Exercise on Episodic Memory in mice

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Episodic memory is a process of retention and reconstruction of knowledge over time for events, events, people, places, objects, and is defined as the memory of events in context, making reference to the fact that information about specific events is linked to the spatial, temporal and situational contexts in which it occurred. The information processing of episodic memory is regulated by the hippocampus and the adjacent cortex. Among the neurotransmitters that regulate the activity of these regions is serotonin (5-HT). The reuptake, recycling and availability of this neurotransmitter is dependent on the activity of the serotonin transporter (SERT), and there is evidence indicating that its expression impacts the mechanisms underlying memory processes. Physical exercise has also been widely reported as an inducer of memory improvement and as a modulator of the serotonergic system. In this context, the aim of this investigation was to evaluate if SERT expression moderates the effect of voluntary exercise on episodic memory. We challenged SERT knockout (KO), heterozygous (HET) and wild type (WT) mice to daily, voluntary physical activity over 8 weeks, and then evaluated episodic memory through the Location Object Recognition (LOR) and Novel Object Recognition (NOR) paradigms, and compared to non-exercise control groups. In addition, evaluated the effects of voluntary exercise on anxious like behavior by Open Field Test (OFT). We found that the execution of voluntary exercise reverses the hipolocomotive and anxious like behavior in mice lacking SERT. In addition, we found that the exercise reverted the difference between SERT WT and HZ rodents observed in control conditions, improving long-term episodic memory in SERT HZ rodents.
Pontificia Universidad Católica de Chile, Universidad de Valparaíso, Núcleo NuMIND, Beca CONICYT Doctorado Nacional, Beca CONICYT Magíster Nacional para Profesionales de la Educación

14) Neuronal morphology and molecular developmental alterations in an OCD mouse model with increased forebrain EAAT3 expression

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Obsessive-Compulsive Disorder (OCD) is a neuropsychiatric disorder characterized by obsessions and compulsions affecting 2-3% population worldwide. Extensive evidence suggests altered glutamatergic transmission in the cortico-striato-thalamo-cortical (CSTC) circuits in OCD. One of the most consistently associated genes in OCD is the *SLC1A1* (solute carrier family 1, member 1) gene encoding the neuronal (epithelial) glutamate transporter EAAT3. EAAT3 is expressed in both pyramidal and GABAergic neurons and prominently in the CSTC circuitry. Recently, our group generated and characterized conditional EAAT3 overexpressing mice (EAAT3glo/CaMKII); this model displays increased anxious and compulsive behaviors. Functional and molecular analysis EAAT3glo/CaMKII showed reduced expression of the NMDA NR2A subunit resulting in an alteration of the NR2B/NR2A ratio and, correspondingly, alterations in the NMDAR-dependent synaptic plasticity at corticostriatal synapses. Here we investigate molecular and functional changes underlying the OCD related behaviors in EAAT3glo/CMKII mice. To this end, we sought to determinea) the changes in the expression of NMDAR and AMPAR subunits and b) neuronal morphology in brain areas relevant to anxiety and compulsivity in the EAAT3glo/CMKII mice across development. Using Golgi-staining, we found that, at postnatal day 30 (p30), prefrontal cortex neurons of EAAT3glo/CaMKII mice have increased both apical and basal dendritic branching compared to control mice. Moreover, we found an increased NR2B/NR2A ratio in EAAT3glo/CamKII mice at p20, but not at p10 suggesting that the EAAT3 overexpression might alter the normal developmental switch of NMDAR subunits. We expect these results would contribute to unravel the molecular synaptic impairments due to altered EAAT3 that might shed light on the pathophysiology underlying OCD

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16) Brainstem catecholaminergic neurons mediate sleep-dependent disordered breathing in heart failure rats

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Sleep disordered breathing (SDB) is the most common co-morbidity in patients with heart failure (HF) and has a significant impact on mortality. Cardiac autonomic imbalance also is a key component of HF pathophysiology, particularly by increased sympathetic outflow. Importantly, pre-sympathetic catecholaminergic neurons (C1) located at the rostral ventrolateral medulla (RVLM) displayed chronic activation in HF condition. Interestingly, we recently found that C1 neurons also contribute to regulate breathing in healthy conditions. Importantly, breathing regularity is regulated in a sleep-state dependent manner. Whether alterations in HF are also sleep-stage dependent has not been previously addressed. Therefore, we aimed to determine sleep-stage dependent changes in breathing regulation in HF and study the contribution of RVLM-C1 neurons on breathing pattern regularity. Male Sprague-Dawley rats underwent volume overload to induce HF. After four weeks of recovery, anti-dopamine β-hydroxylase-saporin (DβH–SAP: 5ng/150nl; or vehicle: NaCl 0.9%/150nl) was used to selectively destroy RVLM-C1 neurons (12.36 mm caudal to bregma, 2.3 mm lateral to the midline, and 8.5 mm below the dura matter). Stainless-steel electrodes were implanted for electroencephalogram recordings (EEG).Breathing and EEG physiological experiments were performed in freely-moving rats. Compared to control rats, HF animals displayed no difference in the total sleep time neither in the time spent in total rapid eye movement (REM) or non-rapid eye movement (nREM) stage. Also, no change in total sleep times were found in rats treated with DβH–SAP. However, the average time spent in nREM epochs (i.e. fragmentation sleep) was lower in HF rats than in control rats (3,9 ± 0,4 vs. 2,1 ± 0,2 min; Sham vs. HF+Veh rats) and partial ablation of RVLM-C1 neurons nREM sleep times (3,2 ± 1,1 min). Importantly, HF+Veh rats displayed irregular breathing at rest both in nREM and REM stages compared to control group and DβH–SAP treatment in HF results in the normalization of breathing variability in nREM and REM to the levels observed in control rats. Our data suggest that irregular breathing is associated to disrupted sleep patterns in HF and that catecholaminergic RVLM neurons contribute to sleep-dependent breathing disorders in HF.

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17) Effect of minocycline on the respiratory response to hypercapnia in mice brainstem slices

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Central chemoreception contributes to adjust breathing to physiological demands and it is essential for maintaining CO_2 and pH homeostasis. Hypercapnic acidosis can activate microglia in the brainstem which may release proinflammatory mediators able to affect the respiratory rhythm; Here we tested whether superfusion of mouse brainstem slices with minocycline, a microglial inhibitor, can affect the basal respiratory rhythm, and the respiratory response to hypercapnia. Brainstem slices were obtained from anesthetized 1-4 days old CF1 mice and superfused with artificial cerebrospinal fluid (aCSF) equilibrated with O_2/CO_2 = 95% / 5% (pH 7.4) at 30 ºC. Fictive respiration was recorded from the ventral respiratory column (VRC) with suction electrodes connected to a differential amplifier. Hypercapnic acidosis (pH 7.2) was performed by switching the gassing of aCSF from 5% to 10% CO_2 equilibrated with O_2. Minocycline (1-30 µM) was added to the superfusion medium and reduced the respiratory frequency (fR) in normocapnic conditions in a concentration-dependent way. In addition, it reduced the CO_2-induced respiratory response. Our results suggest that microglia play a role in the hypercapnia-induced respiratory response.

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18) Altered Wnt signaling in the hippocampus is associated with cognitive impairment in heart failure rats

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Heart failure (HF) is the most common cardiovascular disease in elder population and it is associated with cognitive impairment (CI). CI are likely to result in forgetfulness and poor learning ability which impair treatment adherence and sub-optimal self-care affecting life quality and mortality in HF patients. In HF, CI generally is associated with inadequate O2 supply to the brain due to decrease in the cerebral blood flow (CBF); however, an important subset of HF patients displays neurocognitive decline with no alteration in CBF, and nothing is known about the pathophysiological mechanisms underpinning CI. Therefore, we aimed to study cognitive function in a HF model that shows no change in CBF. HF was surgically induced by volume overload in adult male Sprague-Dawley rats. To evaluate changes in behavior, particularly in learning and memory function, we subjected healthy and HF rats to Morris water maze test. Cardiac echocardiography and carotid artery blood flow doppler was used to determine cardiac diameter and blood flow going to brain, respectively. Wnt-signal, one pathway implicated largely in aging diseases, was assessed in hippocampus micropunches by measuring β-catenin, total GSK-3β and (p-Ser9)GSK-3β expression by immunoblot. Compared to control rats, HF rats display (Control vs. HF): overt signs of cardiac hypertrophy (HW/BW, 2.7 ± 0.4 vs. 4.4 ± 0.5 mg*g−1), but without significative differences in both carotid artery diameter neither in carotid artery blood flow. Importantly, we found that HF rats presented learning impairments and memory loss; increased escape latencies to the target platform along the 5 trials days was observed in HF rats compared to control animals (158.8 ± 1.9 vs.100.0 ± 1.5 % of control, respectively). In Memory flexibility test, control rats continuously decreased the number of trials required to complete the task, whereas rats with HF showed a reduced improvement (4.2 ± 0.1 ± vs. 8.2 ± 1.2 trial, respectively). Finally, compared to control rats, HF rats display (Control vs. HF) a decrease level of β-catenin (100.0 ± 6.3 vs. 79.1 ± 4.3 % of control) along with a reduce level of phosphorylated GSK-3β (100.0 ± 4.8 vs. 62.9 ± 5.9 % of control) indicative of loss of Wnt signaling function in the hippocampus. Taken together, our results indicate that CI in HF rats are i) independent of blood perfusion to the brain; and ii) associated with dysfunction of the Wnt/β-catenin signaling pathway. The mechanisms involved in the alterations of Wnt/β-catenin signaling in HF and its contribution to the development/maintenance of CI deserves future investigations.

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19) Contribution of brainstem oxidative stress on irregular breathing patterns in HF: role of central chemoreceptor neurons

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Enhanced central chemoreflex gain is observed in heart failure (HF) and it is related with breathing disorders and autonomic dysfunction. The Retrotrapezoid Nucleus (RTN) is a major central chemoreceptor area located in the ventral surface of the medulla, that regulate several aspects of breathing including inspiratory amplitude, breathing frequency and active expiration. It has been reported that HF rats displayed elevated levels of reactive oxygen species (ROS) in brainstem areas close to the RTN. Whether ROS play a role in central chemoreflex potentiation (i.e. RTN) and breathing disorders in HF remain to be determined. In previous studies from our laboratory we showed that exercise training (EX) represent a feasible tool to reduced central nervous system ROS levels in HF rats. Therefore, we aim to determine the effect of EX on: i) altered central chemoreflex function, ii) breathing disorders, iii) ROS levels in the RTN of HF rats. HF was induced by volume overload in adult male Sprague-Dawley rats (250 g). Whole-body plethysmography in unanesthetized animals was used to evaluate both resting breathing patterns at rest and chemoreflex function. Central chemoreflex function was assess by the hypercapnic ventilatory response (HCVR) test. Exercise training protocol consist in endurance running on a motorized treadmill (60 min/day, 25 m/min, and 10% inclination) for 6 weeks. The determination of ROS was performed by dihydroethidium (DHE) staining in brainstem sections containing the RTN. Compared to sedentary HF rats (HF-Sed), exercise training HF rats (HF-EX) (HF-Sed vs HF-EX, $p > 0.05$) showed: decreased HCVR ($\Delta VE22.08 \pm 1.15$ vs. 17.51 ± 3.5 ml/min/100g), improved breath-to-breath interval variability (SD1 71.54 ± 4.48 vs. 35.16 ± 4.14 ms; SD2 112.90 ± 14.27 vs. 68.15 ± 4.83 ms), decrease in tidal volume oscillation as measure by the coefficient of variation of VTamplitudes (19.09 ± 0.93 vs. $15.45 \pm 0.58\%$) and an improved breathing irregularity score (27.48 ± 2.73 vs. 8.09 ± 0.92 %). In addition, the RTN of HF-EX rats displayed a reduction DHE staining compared to HF-Sed rats. Our results support the salutary effect of exercise training in HF on normalizing central chemoreflex response to hypercapnia and breathings disorders. In addition, exercise training reduced ROS levels in the RTN suggesting a plausible role for ROS in central chemoreception regulation.

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20) Carotid body denervation improves breathing disorders and normalizes central chemoreflex response in heart failure

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Chronic heart failure (CHF) is global health problem affecting more than 37 million people worldwide. Pathophysiological hallmarks of CHF include cardiac dysfunction and breathing disorders which impact negatively in the prognosis of the disease increasing the risk of mortality. It has been reported that altered chemoreflex function play a critical role in the progression of cardiac failure and appearance and/or maintenance of breathing pattern disturbances in CHF. We recently showed that CHF rats displayed an augmented hypercapnic ventilatory response (HCVR) suggesting a potentiation of central chemoreflex response mediated mainly by the Retrotrapezoid nucleus (RTN). Importantly, it has been reported that peripheral chemoreceptors (i.e. carotid body, CB) determine the respiratory sensitivity of central chemoreceptors to CO2in healthy conditions. Therefore, we aim to determine the potential relevance of this dual chemoreceptor feedback in cardiorespiratory abnormalities present in CHF. Male Sprague-Dawley rats (n=10) underwent volume overload to induce CHF. After two days of CHF induction, rats underwent CB denervation (CHFCBD). Unrestrained whole-body plethysmography and pression-volume conductance catheter were used to study breathing pattern regularity, chemoreflex function (10% FiO2 and7% FiCO2) and cardiac function. Compared to CHFSham, CHFCBD rats (CHFShamvs. CHFCBD) showed a decrease HCVR (5,6 ± 0,5 vs: 3,4 ± 0,2 ΔVe/%FiO2, $P < 0,05$). Also, breathing disorders (i.e. apneas, hypopneas) were significantly reduced in CHFCBDrats (12.0 ± 1,3 vs 4,6 ± 0,7 events/h, $P < 0,05$). Importantly, left ventricle end diastolic pressure (LVEDP) an important measure of ventricular performance was normalized in CHFCBDgroup compared to CHF that do not underwent CB denervation (5,3 ± 0,2 vs 3,7 ± 0,4 mmHg, $P < 0,05$). Together, our results strongly suggest that CB play a critical role in cardiorespiratory abnormalities associated with CHF, possibly through interdependent feedback with RTN neurons.

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21) Acute chemogenetic inhibition of RVLM astrocytes decreases cardiorespiratory chemoreflex response in healthy rats

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The rostral ventrolateral medulla (RVLM) is a region of the central nervous system (CNS) located in the brainstem. Catecholaminergic C1 neurons located in the RVLM are mostly involved in the control of sympathetic outflow; however, C1 neurons are also capable of modulating cardiorespiratory response at rest and during hypoxia. One of the main chemosensory afferences come from the carotid bodies (CBs), which are constantly sensing the levels of O2in the arterial blood. Interestingly, it has been proposed that glial cells of RVLM, mainly astrocytes, display sensitivity to slow changes in tissue PaO2in animals that do not possess CBs, suggesting that these could modulate the cardiorespiratory chemoreflex response to variations in PaO2. However, there is no data of the ability of RVLM astrocytes to induce changes in the chemoreflex response under physiological conditions (i.e. in the presence of functional CBs). In this study, we examined changes in the cardiorespiratory chemoreflex response to hypoxia (FiO210%) and hypercapnia (FiCO27%) in male Sprague-Dawley rats before and after acute inhibition of RVLM astrocytes. A dose of sodium cyanide (NaCN, 1 mg/kg) was administered to examine the contribution of the CBs on the chemoreflex response. Whole body plethysmography was used to study breathing patterns and blood pressure radiotelemetry was used to study cardiovascular changes. Stereotaxic bilateral injection of an inhibitory Designer Receptors Exclusively Activated by Designer Drugs (DREADD) was used to selectively inhibited RVLM astrocytes. After DREADDs activation with Clozapine-N-Oxide (CNO, 1 mg/kg i.p.), we observed a decrease in both hypoxic and hypercapnic ventilatory response (HVR and HCVR) (3.3±0.2 pre CNO vs 2.1±0.3 post CNO ΔVE/%FiO2and 6.2±0.3 pre CNO vs 4.0±0.2 post CNO ΔVE/%FiCO2, respectively), but also a decrease in resting normoxic ventilation (25.6±0.9 pre CNO vs 14.4±0.8 post CNO ml/min/100g). Interestingly, there is no significant changes in ventilatory patterns when CBs are stimulated after RVLM astrocytes inhibition. In addition, we observed a decrease in cardiovascular function after inhibition, specifically by a drop in blood pressure (122.7±7.2 pre CNO vs 103.9±6.1 post CNO mmHg) but not in heart rate following CBs stimulation. Our results suggest that RVLM astrocytes may have an important role in modulating the cardiorespiratory chemoreflex response in physiological conditions.

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22) Cultured brainstem astrocytes and microglia increased their intracellular calcium concentration in response to gliotransmitters and hypercapnic acidosis

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Central respiratory chemoreception is essential for adjusting respiration to the physiological demands, and to keep CO_2 and pH homeostasis in the brain. Previously, it has been described that astrocytes from the ventral surface of the brainstem, specifically in the retrotrapezoid nucleus, increase intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) and release ATP in response to hypercapnic acidosis. We saw that astrocytes from the caudal part of the brainstem release D-Serine, ATP, and glutamate in response to hypercapnic acidosis *in vitro*. Here we evaluated whether microglial cells from brainstem are chemosensitive and increase $[Ca^{2+}]_i$ in response to gliotransmitters and hypercapnic acidosis. Neonatal mouse astrocytes and microglia in primary cultures from brainstem were incubate with Oregon Green BAPTA-1 for 45 min. Ca^{2+} fluorescence fluctuations were record with a digital CMOS camera (Hamamatsu, ORCA-Flash 4.0 V2) mounted on a Nikon FN1 epifluorescence microscope. Basal condition corresponds to superfusion of the cells using artificial cerebrospinal fluid (aCSF) equilibrated with 5% CO_2. Normocapnic acidosis was reach with aCSF 5% CO_2 with HEPES, pH 7.0 and the hypercapnic acidosis by increasing the superfusion medium gassing of CO_2 from 5% to 10% CO_2. Gliotransmitter (D-serine, glutamate, and ATP) were add into the superfusion medium. We observed that brainstem astrocytes and microglia in primary cultures increased their $[Ca^{2+}]_i$ in response to normocapnic and hypercapnic acidosis, as well as, in response to gliotransmitters. These results show that the astrocytes and microglia from caudal part of the brainstem are chemosensitive and could contribute to the respiratory response to hypercapnic acidosis. These results are relevant to understand respiratory-related disorders in which central chemoreception plays a significant role.

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23) Expression of CB1R on respiratory-related brainstem nuclei

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The pattern of respiratory rhythm is generated by a neural network in the brainstem and its neuromodulation is exerted by activation of different receptors, among them the cannabinoid type 1 receptor (CB-1R). CB-1R is widely distributed in the central nervous system, including the brainstem and has been involved in the inhibition of the respiratory rhythm; however, there is not clarity on the cell types within respiratory-related nuclei which express CB-1R and the mechanisms that influence breathing are unclear. Here we explore CB-1R distribution on astrocytes, neurons, and endothelial cells in different respiratory-related nuclei using immunofluorescence in brainstem cross sections (30 mm thick) obtained from CF1 adult mice. We found neurons (neu-positive/CB-1R-positive cells) and astrocytes (GFAP-positive/CB-1R positive cells) in the nucleus tract solitary (NTS), hypoglossal nucleus (XII), raphe nucleus (RN) and ventral respiratory column (VRC) at stereotaxic level approximately -6.84 from the bregma. In addition, we found CB-1R expression on endothelial cells around and within the NTS, XII, VRC and RN. Our results suggest that possible mechanisms explaining the inhibitory effect of cannabinoids on the respiratory rhythm should include different cellular types beyond neurons.

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24) Sensory neurons from nodose ganglia express Cyclin-dependent kinase 5, its activators and its targets involved in pain signaling

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The nodose ganglia (NG) contain the cell bodies of most sensory neurons of vagus nerve. NG neurons innervate and sense stimuli from viscera and convey this information to the central nervous system through visceral afferents, contributing to visceral pain. Cyclin-dependent kinase 5 (Cdk5) plays a fundamental role in several physiological and pathological processes in nervous systems, including its function in sensory neurons from trigeminal and dorsal root ganglia, where it phosphorylates several targets involved in pain signaling, such as transient receptor potential vanilloid 1 (TRPV1) and nucleotide P2X receptor subunit 2 (P2X2). However, there is no evidence of the expression and function of Cdk5 in NG. Therefore, we evaluated the expression of Cdk5, its activators (p35 and p39), and its substrates (TRPV1 and P2X2) in mouse NG. NGs were excised from anesthetized (ketamine/xylazine 75/7.5 mg/kg) adult mice, fixed in 4% paraformaldehyde, cryoprotected in sucrose 30%, embedded in Tissue-Tek and sectioned (12-20 µm) in a cryostat. By immunofluorescence, using specific primary antibodies against Cdk5, p35, p39, P2X2, P2X3 and TRPV1, we demonstrate for the first time the expression of Cdk5, p35 and p39 in NG neurons (betaIII-tubulin positive cells). In addition, we showed that TRPV1, P2X2 and P2X3 are expressed in high number of NG neurons, as previously described. Altogether, these results demonstrate that NG neurons express Cdk5 and its activators, suggesting that Cdk5 might be functional, thus playing a potential role in NG sensory neuron functions.

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25) Lack of Skin Cell-secreted Neurotrophic Factors results in a Small Fiber Neuropathy

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Introduction: Small-fiber neuropathy (SFN) is the result of dysfunction of the small unmyelinated fibers that innervate the skin. SFN is one of the most frequent and troublesome complications of Recessive Dystrophic Epidermolysis Bullosa (RDEB). Intraepidermal fibers degenerate in the skin of RDEB and fail to regenerate. In this study we aim to investigate the mechanisms behind this failure by focusing on neurotrophins secreted by skin cells. We will use a wide range of assays, spanning from in vitro, animal models and patients skin biopsy, to determine the specific neurotrophic factor that is lacking for a normal regeneration of skin fibers in RDEB. Once the factor is identified, we will intend to use it as a therapeutic option for SFN in RDEB Material and Methods: Isolation and Culture of Primary Human Keratinocytes and Fibroblast from Adult Human Skin healthy and RDEB patients. Also, HaCaT cell line were used to in vitro wound healing assays. Rat DRG were exposed to keratinocyte conditioned medium (K-CM) to induce axonal regeneration. Cultures were subject to axonal transection to produce an injury by axotomy. Expression of neurotrophic factors and TRKs mRNA qRT-PCR. Axonal regeneration analyzed by immunostaining. Results: Healthy keratinocytes and fibroblast in vitro wound healing increase the expression of neurotrophic factors mRNA after 24 and 48 hrs. DRG neuron and axons following axotomy K-CM treatment increased the regeneration rate compared with negative controls-treated explants, suggesting that K-CM scratched increase of NTFs to stimulate axonal regeneration in vitro. Discussion: Here, we show that K-CM after wound in vitro increase the expression of neurotrophic factors mRNA to promote axonal regeneration after injury in the DRG. This opens a new dimension in our understanding of small fiber neuropathy. Debra Internacional

26) Dissecting the Contribution of Reactive Astrocytes to Myelin Repair

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Myelin speeds up action potential transmission, allowing for efficient functional integration in the central nervous system (CNS). In demyelinated diseases, such as Multiple Sclerosis (MS), myelin is loss in several CNS areas. After a demyelinated insult, there is a spontaneous repair process (remyelination) characterized by the migration, proliferation, and differentiation of oligodendrocyte precursor cells (OPC) into remyelinating oligodendrocytes (OL). In addition to this dynamic response of the oligodendroglia population, a highly conserved hallmark of demyelinated lesions is the massive recruitment of reactive astrocytes. Astrocytes release several molecules that can modify OPC proliferation and differentiation, potentially affecting OL production and the consequent myelin synthesis. Current evidence indicates a role for reactive astrocytes on the demyelination/remyelination process. However, the precise cellular mechanisms and the contribution of reactive astrocytes to myelin repair is not completely understood. To dissect the role of reactive astrocytes at different stages of remyelination, we use the lysolecithin (LPC)-induced demyelinated lesions model in the mouse corpus callosum (CC). Thirty days before LPC stereotaxic injection into the CC, astrocytes are infected with a lentivirus encoding SOCS3 (lenti-SOCS3) to inhibit the JAK-STAT3 pathway and prevent astrocyte reactivity. The effects of this genetic inactivation of astrocyte reactivity are being analyzed by the quantification of OPCs and OLs at different time points of the remyelination process by using immunohistochemistry and confocal microscopy on post mortes sections. Longitudinal magnetic resonance imaging (MRI) of mice injected with LPC and lenti-SOCS3 are also being performed to image and quantify myelin loss and repair. Our results will shed light on glia-glia interactions involved in myelin disorders such as MS.

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27) Expression analysis of long non-coding RNAs in the human brain

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Human brain is organized in local and large-scale connections that are fundamental for its functioning (Fornito et al., 2016). Such organization allows the emergence of complex phenomena as cognition and behavior. Moreover, clinical and neurodegenerative disorders have been associated with the alteration of brain network organization, as in Alzheimers or Schizophrenia (Crossley et al, 2014). The cytoarchitecture diversity that supports this structural organization is the outcome of the differential gene expression programs in nerve cells distributed along the brain during specific stages of the development (Hawrylycz et al., 2015). Among these genes, non coding RNAs (ncRNAs) exert a precise control over neural networks in different levels (Zampa et al., 2019). Specifically, more than 40% long non-coding RNAs (lnc-RNAs) are expressed in the brain (Derrien et al, 2012). It has been reported that lncRNAs participate in a plethora of neuronal processes as neurite elaboration, synaptogenesis, neural plasticity (Briggs et al, 2015). However, their distribution and specificity along different regions of the Human Brain has not been characterized so far. In this work, we used the Allen Human Brain Atlas to map lncRNAs along different brain regions. Microarray probes were re-annotated from the database following the pipeline from our group (Amaral et al., 2018), this allowed us to annotate almost twice the number of probes associated to lncRNAs than the former annotations. Additionally, we analyzed the differential expression of long non-coding RNAs for different areas along the brain. Our results indicate that the correlation in lncRNAs expression between areas exponentially decreases as the distance among areas increases, as it has been previously reported for protein-coding genes.

28) Peripheral inflammatory biomarkers and risk of dementia in the Chilean GERO cohort

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Introduction: In Chile, dementia is one of the most important causes of disability in elderly, corresponding nearly to 40% of cases. Many basic and relevant questions remain unanswered in Chile, including what specific age-related factors predispose some individuals to develop neurodegenerative diseases (pathological aging) versus healthy aging. The answer likely involves several factors including peripheral components and cognitive complaint. Peripheral inflammatory biomarkers may play an important role in cognitive decline associated with pathological aging and incidence of Alzheimer´s disease (AD). We propose to study the risks factors associated with pathological aging in a Chilean cohort. Material andMethods: We evaluated and quantified plasma samples derived from the GERO cohort (58 elderly subjects with cognitive complaint, >70 years), 25 healthy controls and 22 Alzheimer's patients. Neuropsychological tests were applied to all subjects. We assessed several inflammatory biomarkers using Luminex technique including IL-2, IL-6, IL-10, TNF-α, CRP y SAP. Results: The AD group was significantly older (p=0.04). The cognitive complaint and controls groups had a higher proportion of females to males than AD group (p=0.02). Frequency of the APOE-e4 allele, was substantially higher in MCI and AD patients than controls (p=0.002). Significant differences were observed in plasma TNF-α (p=0.03) and CRP (p=0.01) levels among the three groups. We observed statistical differences in neuropsychological tests between the three groups in the Addenbrook´s Cognitive Examination (ACE) which evaluated attention, orientation, memory, fluency, language and visuospatial skills, the Free and Cued Selective Reminding Test (FCRST) that to control attention and cognitive processing to identify memory impairment and The Ineco Frontal Screening (IFS) that is a screening tool to detect executive dysfunction. IL-6 and TNF-α levels were associated with poorer performance in memory through FCSRT, even after adjusting for variables such as age, sex, education and APOE-e4 allele. Discussion: Our work will allow us to determine the risks factors associated with the prognosis of elderly with cognitive complaint on the evolution to a significant functional decline. The GERO cohort will help design public health policies to prevent aging disease, and contribute to a better understanding of functional decline associated with cognitive impairment and dementia.

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29) Effect of systemic inflammation and aging on the expression of TREM2 in the brain of APP/PS1 mice

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the presence of senile plaques and neurofibrillary tangles in the brain. These protein aggregates are associated with inflammation and activation of microglia and astrocytes. Microglia are the main cell responsible for the neuroinflammatory response, production of reactive oxygen species (ROS), as well as phagocytosis and clearance of β-Amyloid (Aβ). Under chronic inflammatory conditions, such as in aging, microglial phagocytic and Aβ clearing capabilities are hindered, and their activation becomes cytotoxic. After inflammatory stimuli, such as LPS injection, microglia activate, releasing cytokines associated with neuroinflammation and ROS. An animal model for the study of AD is the APP/PS1 mouse, which overexpresses mutated presenilin and a mutated humanized form of APP, processed and aggregated in Aβ plaques. Microglial activation is a complex process in which several receptors and signalling pathways are involved, among which is the "triggering receptor expressed on myeloid cells 2" (TREM2). TREM2 ligation activates DAP12, which in turn initiates a signalling cascade that includes phosphatidylinositol 3-kinase (PI3K), Akt, mitogen-activated protein kinases (MAPK/Erk1-Erk2) and increases in intracellular calcium levels. TREM2 ligands include polyanionic molecules such as LPS, and other microbial products, apolipoproteins, as well as Aβ. TREM2 has been associated with the phagocytic activity of microglia, as well as with the modulation of inflammatory signalling, microglial proliferation and survival. Currently, there is conflicting evidence of the role of TREM2 in AD and Aβ deposition. We hypothesize that TREM2 expression and activation is modified by age and systemic inflammation due to the activation of proinflammatory pathways. To characterize changes in the expression and activation of TREM2, brain samples were obtained from juvenile and adult (3 and 12 m, respectively) WT and APP/PS1 C57 mice, 24 h after being treated with an intraperitoneal injection of LPS (0.5mg/Kg). Protein expression of TREM2 was analysed through SDS-PAGE Western-Blot, and genetic expression was analysed through qRT-PCR. The distribution of TREM2 was determined by immunohistochemistry, and the inflammatory activation by ELISA of inflammatory cytokines. Levels of TREM2 protein and mRNA are increased by aging and inflammatory conditions, which correlates with increased levels of TNFa after LPS injection. Our results confirm age-related changes on TREM2 and suggest that TREM2 plays a role in neurodegenerative disorders-associated inflammatory activation of microglia.

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30) Early increase of serine racemase expression in mice with proinflammatory brain environment

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Aging, the main risk factor for neurodegenerative diseases such as late-onset Alzheimer disease (LOAD), is characterized by a neuroinflammatory environment. Our "glia-dysregulation hypothesis" proposes an aging-associated impairment on glial cell regulation causes LOAD by promoting a neurotoxic neuroinflammatory environment. Given that the excess on D-serine promotes NMDAR-mediated neurotoxicity, and the expression of serine racemase (SR; the enzyme synthesising D-serine) is increased in inflammation, we assessed the expression of SR in the brain during aging and after an acute systemic inflammatory stimulus in C57 wild type (WT) mice and in two models with chronic neuroinflammation, the Scavenger Receptor A Knock Out (SRAKO) mice, which show elevated pro-inflammatory cytokines and reduced Aβ uptake, and the double transgenic mice expressing humanized mutated amyloid precursor protein and mutated presenilin 1 (APP/PS1). Juvenile, adult and old (3-, 12-, and 20-month old, respectively) C57 WT, SRAKO and APP/PS1 mice received a single i.p. injection of vehicle (PBS) or 0.5 mg Kg-1 LPS, to induce systemic inflammation. Animals were perfused 24 h later with Hank's to obtain brain lysates, or with PBS and fixative for morphological studies. SR content was measured by western blot, and its distribution in association to NeuN and GFAP was evaluated by immunofluorescence in 20 µm brain sections. We found an aging-associated increase in the SR expression in WT brain lysates, increasing up to 1.5- and 2.0-fold, respectively in adult and old mice compared with juvenile mice. Inflammation after i.p. LPS induced a robust increase of SR expression in juvenile and adult mice, reaching similar levels to those found in old mice. Histological studies revealed that SR was nearly undetected in the hippocampus of juvenile WT mice. However, SR associated with NeuN immunolabeling in the stratum pyramidale of CA3 was 4- and 8-fold larger in juvenile SRAKO and APP/PS1 mice, respectively. A conspicuous aging-dependent increase of SR associated with NeuN in the stratum pyramidale of CA3 and CA1 in adults and old mice of all genotypes, reaching up to 40-fold the expression observed in juvenile mice. Systemic inflammation promoted the increase in SR associate to GFAP at all ages. Our results reveal that the expression of SR increases with aging- and under inflammatory conditions. The elevated expression of SR observed already in the juvenile transgenic mice may facilitate D-serine- and glutamate-induced excitotoxicity, facilitating neurodegeneration and perharps promoting LOAD pathogenesis.

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31) Effect of aging on the Fractalkine (CX3CL1) - CX3CR1 axis signaling in wild type and the inflammatory mouse model SRA-KO

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Introduction: Currently, the way Fractalkine/CX3CR1 signaling changes during the lifespan and which role it may have in aging is not well defined. Fractalkine is a dual-acting chemokine, because its soluble form exerts a pro-inflammatory effect and the form adhered to membrane is anti-inflammatory. Here, we aim at characterizing age-dependent changes of Fractalkine/CX3CR1 pathway in the brain of wild type (WT) and a neuroinflammatory mouse model knockout for the scavenger receptor A (SRA-KO). Material and Methods: WT and SRA-KO mice at various ages (3-, 6-, 12- and 20-month old) were analyzed. To evaluate the effect of inflammation, mice were administered intraperitoneally 1 mg/kg of LPS or PBS (vehicle). 24 hour later, the relative presence at the protein level of Fractalkine and CX3CR1 was analyzed by western blot. Brain localization and distribution of both proteins was assessed by immunohistochemistry. Statistical analysis was done by non-parametric tests (Kruskall-Wallis & Man-Withney). Results: In 3- and 6-month-old mice brains, Fractalkine/CX3CR1 signaling levels were unaffected regardless of genotype (WT or SRA-KO) or inflammatory condition. In contrast, at 12 months of age, levels of Fractalkine increased up to 3-fold compared with young mice, with predominance of the soluble fraction (proposed as pro-inflammatory). The increased presence of Fractalkine decreased in 20-month-old mice, without reaching the values observed at 3 and 6 months of age. The absence of SR-A favor the accumulation of β-amyloid (Aβ). In addition, Aβ activated the extracellular matrix favoring the expression of soluble Fractalkine and promoted proinflammatory activation. Discussion: Our findings suggest that aging is a condition that favors the presence of Fractalkine in its extracellular soluble (cleaved) form. Thus promoting microglial inflammatory activation and the neuroinflammatory environment of senescent microglia.

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32) Aging affects Smad-dependent and -independent TGFβ signaling in microglia

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Microglial cell activation can result in neuroinflammation. Microglial phenotype can be modified from a cytotoxic to a protective pattern by the cytokine TGFβ1, which modulates neuroinflammation and cytotoxicity. TGFβ1 activates canonical signaling involving Smad, and Smad-independent signaling. Smad signaling regulates the activation of microglia, decreasing inflammatory cytokines and reactive oxygen species (ROS) levels, and inducing Aβ phagocytosis. Thus, Smad3-TGFβ1 signaling appears to promote a protective microglia phenotype. Aged subjects have increased levels of TGFβ1. However, inflammation-induced Smad activation is reduced. A lower Smad3 activation with high levels of TGFβ could result in an increased activation of the non-canonical pathway, which could favor the inflammatory activation of microglia. Therefore, we hypothesize that dysregulation of TGFβ signaling, with increased activation of non-canonical pathway could promote neuroinflammation in aged individuals. In addition to non-Smad pathways, NFκB is a transcriptional factor that activates in response to oxidative stress and inflammation. The interaction between NFκB and Smad in microglia during aging and inflammation, remains unclear. We observed that Scavenger Receptor class A (SR-A) mediates Aβ phagocytosis, as well as inflammatory activation of glial cells. SR-A deficiency induces accumulation of Aβ, increases levels of TNFα, while TGFβ levels decrease. 3- and 12-month old C57 WT and SR-A-KO mice, were treated with intrathecal administration of 30 or 100 ng of TGFβ1, or vehicle, under control or systemic inflammatory condition (ip injection of 0.5 mg/Kg LPS). Brain lysates were obtained 24 h post injection for western-blot of canonical and non-canonical pathways proteins. mRNA was extracted to perform qRT-PCR of transcripts associated with these proteins. TNFα levels were assessed by ELISA. To evaluate Smad signaling, microglial cell line (BV2) cultures were treated or not with SN50 (NFκB inhibitor), and subsequently with LPS or PBS. Our results show that in WT and SRA-KO mice, aging is associated with a decrease in Akt, JNK, and pJNK levels. Decreased pJNK was observed in juvenile SRA-KO mice after LPS treatment, compared to control. No change was found for total nor activated Erk, and p38, in either genotype, age or treatment. JNK, AKT, ERK, and P38 play an important role in many inflammatory diseases, therefore, its study is important as they can regulate proinflammatory cytokine synthesis such as IL2, IL6 and TNFα, potentially modifying microglial phenotype to a more reactive, and neurotoxic phenotype in aged subjects.

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33) Relevance of the Scavenger Receptor-A for the neurotoxic outcome of the inflammatory activation on hippocampal cells

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Aging, characterized by chronic neuroinflammation and increased oxidative stress, is the main risk factor for Alzheimers disease (AD). Moreover, Neuroinflammation is a conspicuous actor even at early stages of AD. Our "glia-dysregulation" hypothesis for AD proposes that age-dependent changes of microglia activation are critical for AD pathogenesis, resulting in an aberrant activation of microglia leading to neuroinflammation, neuronal dysfunction, and eventually to increased neurotoxicity and neurodegeneration. Scavenger receptor A (SR-A), involved in β-amyloid (Aβ) uptake and glial cell activation, has emerged as a key actor in AD. Thus, we aimed at assessing the participation of SR-A in the mechanisms leading to the neuroinflammation observed in aged individuals, at the level of activation of intracellular signaling and the production of inflammatory mediators. We observed by western blotreduced SR-A protein levels by 50% in adult (12-month-old) compared with young (3-month-old) wild-type (WT) mice. A similar reduction was also observed in a transgenic mice that accumulates Aβ (APP/PS1). We analyzed the plasmatic levels of inflammatory cytokines in young and adult WT, APP/PS1, SR-A Knock out (SR-A-/-) and triple transgenic mice (APP/PS1/SR-A-/-) by ELISA, and detected increased pro-inflammatory cytokines (TNFα and IL1β) levels. IL1β was 3-fold higher in adult APP/PS1/SR-A-/- respect to adult WT and young APP/PS1/SR-A-/- mice. A similar result was observed for TNFα. Then, we compared by RT2 Profile Arraythe mRNA levels of several genes involved in neurotoxicity on WT, APP/PS1, SR-A-/- and APP/PS1/SR-A-/- mice, to evaluate the role played by SR-A in the profile of cell activation. We observed a significant variation of the levels of several genes in APP/PS1/SR-A-/- miceat different ages. Levels of Gpx1, Sod1, Nfkb1, Tgfb1, Rap1a and Chuk were downregulated in adult compared with young mice. We also observed the downregulation of Gpx1 and Chuk on APP/PS1 adult compared with APP/PS1 young mice, and the upregulation of Nos2 and Stat1 at the same condition. When we analyzed the levels of mRNA of WT compared with APP/PS1/SR-A-/- at both ages, we detected the upregulation of Gpx1, Sod1, Nfkb1, Rap1a and Stat1. Finally, we observed a robust upregulation of Msr1 on SR-A-/- and APP/PS1/SR-A-/- compared with WT mice at all. Interestingly, the overexpression of Msr1 in animals lacking SR-A decreased as mice aged. Our results show that SR-A participates in the regulation of neuroinflammatory cell activation.

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34) Phenotypical differentiation (M1/M2) of brainstem microglia induced by hypercapnia

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Breathing, essential motor behavior for life, is generated by the respiratory pattern generator (RPG), a neural network distributed along the ventral (VRC) and dorsal (DRC) respiratory columns of the brainstem. The GPR is modulated by cells capable of detecting changes in CO_2 and H^+, located within the RPG or in nuclei that project towards it. Since microglia are cells that are functionally related to neurons and astrocytes, and these in turn, release substances able to activate microglia, we study whether the brainstem microglia of CF1 mice challenged with prolonged hypercapnia show phenotypic changes, both in vivo and in vitro, characteristic of a proinflammatory phenotype. The microglia morphology was evaluated in brains by using immunofluorescence for detecting Iba-1, a microglia marker, and the CD86 or CD206 membrane proteins, M1 and M2 microglia phenotype markers, respectively. Mice were exposure to 90 minutes of inhalation of pure air (controls) or air enriched with 10% CO_2 for 30 minutes, followed by 60 minutes of pure air. In addition, pure cultures of brainstem microglia were exposed to 10% CO_2 in air for 2 hours. In these cultures, detection of Iba-1, CD86, CD206 and the ELISA measurement of concentrations of IL-1β and TGF-β, cytokines released by microglial phenotype M1 and M2, respectively, were performed. We found that the microglia of brainstem chemosensitive nuclei, but not those from SP5 nuclei or cortex, reduce the number of branches, and increase the size of their cell bodies, associated with the increased expression of CD86, but not CD206. Besides, microglia exposed to high PCO_2, release to the culture medium increased levels of IL-1β. Our results suggest that microglia may have a role during high PCO_2 states, perhaps down-regulating the respiratory rhythm.

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35) Astroglial connexin hemichannels as novel targets for the treatment of depression

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Studies suggest that astrocytes may be involved in the pathogenesis of depression, but the mechanisms remain unclear. Recent studies have suggested that Connexin 43 hemichannels (Cx43 HCs), which mediate the release of gliotransmitters from astrocytes into neuronal synapses, may increase their activity in depressive patients and after chronic restraint stress in rodents - a commonly used animal model for depression. Astroglial Cx43 HCs have also been shown to decrease their activity *in vitro* in response to antidepressants. Here, we set out to determine whether pharmacological blockade of Cx43 HCs can induce antidepressant effects. Intra-hippocampal microinjection of TAT-Cx43L2, a peptide capable of selectively blocking Cx43 HCs without affecting Cx43-dependent gap junctional activity, induced antidepressant effects, which were prevented by co-injection with glutamate and D-serine. Incubation with the peptide decreased in NMDAR activity in hippocampal slices (which included astrocytes) but not in primary hippocampal neurons (void of astrocytes). The effects of the peptide on hippocampal NMDARs was prevented by incubation with glutamate and D-serine. By using structure-based virtual screening of small molecule libraries we identified a small molecule with low free binding energy that was capable of binding to the connexin 43 C-terminal as assessed using plasmon resonance and showed potent Cx43 hemichannel blocking effects *in vitro*, as assessed by dye uptake in HeLa cells transfected with Cx43 and in an astroglial cell line. Systemic administration of this molecule induced fast antidepressant effects (within 10 minutes) in the forced swim and tail suspension tests, without inducing sedative effects, in rats that underwent previous chronic restraint stress. The molecule also induced a significant decrease in NMDA receptor-mediated activity in rat hippocampal slices, which could be prevented by addition of glutamate and D-serine. The present results propose astroglial Cx43 hemichannels as a new pharmacological target for the treatment of depression, via an NMDA receptor-dependent mechanism similar to NMDAR antagonist ketamine, but without its sedative effects.

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36) Transcriptomics architecture predicts Claustrum functional involvement in mild chronic stress disorder: A functional genomics, behavioural and cellular approach

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Claustrum is considered a multisensory structure due to its connectivity with different brain nuclei. However, its function is not entirely clear, in part, due to its complex morphology and intricate topology, aspects that hinder access for electrophysiological activity registration and functional lesion evaluation. On the other hand, stress produces sensory deprivation as it impairs the functioning of sensory systems such as audition and olfaction. In turn, other nervous system structures and circuits that establish direct or indirect connection with the Claustrum are also affected by stress. Therefore, in this work it is proposed that the Claustrum is a central nucleus in the stress response control. Through a bioinformatic analyses we have characterized Claustrum functional genomics enrichment, identified marker genes for this structure, such as Nurr1 and Prss12, and genomic networks associated with stress and mental disorders. Therefore, we assessed the immunoreactivity of Nurr1 and Prss12 in the Claustrum of rats exposed to unpredictable chronic stress (CUS) compared to controls. In addition, we associated the immunostaining of these proteins with plasma corticosterone levels, anxiety and depressive behaviors. These immunohistochemical and structural analyses of Claustrum exhibited changes in cell morphology, associated with some trends that would indicate alterations in Nurr1 and Prss12 neuronal expression patterns in the Claustrum. More importantly, we were able to show that these modifications are positively associated with the response of physiological stress markers, such as the response of corticosterone to a stress stimulus (forced swimming; Spearman correlation $p<0.005$; $r=0.829$), locomotor activity (Spearman correlation $p<0.005$; $r=0.886$) and performance in the elevated-plus maze (Spearman correlation $p<0.005$; $r=0.886$). It is remarkable that these associations were observed in the medial tier of the Claustrum, which involves the two main nuclei of the Claustrum: endopiriform and dorsal Claustrum. Therefore, we concluded that the Claustrum responds early to the effect of an unpredictable chronic stress model or to mild stress levels by modifying its structure and the expression of molecules associated with the stress response.

37) Chronic stress impairs functional connectivity in the prefrontal-hippocampal axis during acquisition of spatial reference memory

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Spatial reference memory (SRM) is a complex cognitive process that allows remembering of relevant locations in the environment. This cognitive function Is supported by several brain structures, including the prefrontal cortex (PFC) and the hippocampus (HPC). Recent studies have shown, through local field potential (LFP) recordings in freely-moving mice, that spectral coherence, a measure of functional connectivity, increases gradually in the PFC-HPC neural network throughout the acquisition of SRM. In addition, previous studies have shown that chronic stress modifies functional connectivity in the PFC-HPC network in anesthetized mice. However, it is unknown whether chronic stress alters PFC-HPC synchronization during the acquisition of SRM. To address this issue, C57BL/6 mice were chronically implanted with electrodes in the PFC and the HPC, and then underwent restriction stress for seven consecutive days. Control mice were not subjected to stress. Mice from both groups underwent the LFP recording during the acquisition of the SRM in the Barnes maze. We found that chronically stressed animals showed a slower acquisition during navigation and less retention of long-term memory. At a neurophysiological level, chronically stressed animals showed decreased spectral power in the theta (6-10 Hz) and slow gamma (20-40 Hz) band in the PFC and decreased PFC-HPC spectral coherence in the same frequency bands during acquisition of the SRM. These results suggest a key role of functional connectivity in the PFC-HPC network during acquisition of SRM and establishes a network mechanism for the effect of chronic stress on cognitive functions.

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38) Cotinine counteracts the CS-induced morphological changes in astrocytes and stimulates the activity of the JAK/STAT after chronic stress in mice

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Chronic stress (CS) is a public health problem worldwide, it affects all social and age groups. Intense, repeated or uncontrolled stress has been implicated in the appearance of multiple neuropsychiatric conditions. In the hippocampus and prefrontal cortex, CS decreases the density of astrocytes and alters their morphology and function. This type of disorder, which also causes depression, is treated with selective serotonin reuptake inhibitors. Animal stress models have recapitulated glial abnormalities that are comparable to the human condition, proving useful for investigating molecular mechanisms and the effectiveness of medications for CS. Cotinine, a tobacco-derived alkaloid, facilitates the extinction of fear, decreases depressive and anxiety behaviors, improves memory and restores astrocytic density in the hippocampus and frontal cortex in mice subjected to fear conditioning or with chronic stress. Here, we investigate the effect of cotinine on the morphology of astrocytes in CS. C57BL/6 mice were divided into 3 groups: 1. Stress-free control + IN buffer saline (PBS); 2. CS + PBS; 3. CS + Cotinine. After CS, the mice were tested for depressive behavior. Cotinine counteract the CS-induced morphological changes in astrocytes, and stimulates the activity of the JAK/STAT pathway in the hippocampus. These changes were accompanied by a decreases in depressive behavior after CS.

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39) Paradoxical effects of glucocorticoids in anxiety at the rat insula

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Glucocorticoids (GCs) are released from the adrenal glands in response to stress, but its effects on anxiety appear paradoxical, with studies suggesting anxiolytic and other anxiogenic effects. The present study aims at determining the effects of short term (<5 min) GCs (corticosterone, CORT) at the rat insula in anxiety, by using two different anxiety-like behavioral paradigms; the elevated plus maze (EPM) and hyponeophagia. The pharmacological blockade of adrenal GC synthesis by metyrapone induced anxiolysis, suggesting that basal CORT is anxiogenic. A low dose of intra-insular corticosterone prevented the anxiolytic effects of metyrapone, suggesting that the insula is a critical brain site for the actions of GCs in anxiety. However, a greater dose, intra-insular CORT induced anxiolysis. In untreated rats, low doses of intra-insular CORT induced anxiolytic effects in both the EPM and hyponeophagia, and in the latter, an arousing context required a larger amount of intra-insular CORT to induce anxiolytic effects, suggesting that greater the arousal, greater the dose of CORT needed to induce anxiolysis. Intra-insular CORT did not affect CORT blood levels and had anxiolytic effects despite blockade of adrenal GC synthesis, suggesting that its anxiolytic effects are not dependent on the regulation of the HPA axis. Intra-insular GC receptor antagonist mifepristone had no effect on CORT-induced anxiolysis, while microinjection of mineralocorticoid receptor antagonist spironolactone prevented the anxiolytic effects of CORT and induced an increase in anxiety when injected alone. CORT covalently attached to BSA to restrict its effects to the membrane showed anxiogenic effects at all doses. The present results suggest two competing mechanisms that modulate anxiety at the insula; an anxiogenic membrane-dependent mechanism and an anxiolytic mineralocorticoid receptor-dependent mechanism.

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40) Effects of AM251 and Polyunsaturated Fatty Acids n-6 on Decision-making, impulsivity and attention of stressed rats

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Decision-making, impulsivity and auditory attention are complex cognitive functions that allow individuals to respond effectively to environmental threats. In rats, both chronic stress and supplementation with polyunsaturated fatty acid (PUFA) n-6,in a dose of 1 ml/kg/day, impair these cognitive functions while administration of AM251, an inverse agonist of the cannabinoid receptor type 1 (CB1), in a dose of 0.3 mg/kg of animal weight, counteracts the effect of stress in these cognitive functions. In this scenario, the main objective of this investigation was to evaluate the effects of AM251 administration on cognitive functions in adolescent rats that were supplemented with n-6 PUFA and stressed chronically. Male *Sprague Dawley* rats were trained in the Two-alternative choice task (2-ACT) paradigm. This behavioral task allows quantifying complex cognitive functions such decision-making, impulsivity and auditory attention in rodents. After learning the 2-ACT, animals were separated into four experimental groups: “No stress”, which were injected intraperitoneal with vehicle (physiological serum + 1% ethanol) and orally supplemented with 800 microliters (µL) of water; “Stress” group, had the same treatment as the previous group but were chronically restrained stressed; finally, “Stress + PUFA n-6 + AM251” and “No stress + PUFA n-6 + AM251” groups in which the animals were treated with PUFA n-6 and AM251. The rats in the stress group showed a significant deterioration of the attention with respect to the animals of the No Stress group, while the treatments with PUFA n-6 and AM251 counteracted the effect of stress on auditory attention. These results suggest that the CB1 receptor plays a role the effects of stress and n-6 PUFA on executive functions such as attention. This study will open new ways to find pharmacological targets for the treatment of neuropsychiatric diseases related to stress.

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41) Cross-areal spectral coherence in anxiety-related serotonergic networks in mice

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The serotonergic (5-HT) system targets several brain regions involved in the pathophysiology of anxiety-related disorders. Accordingly, functional connectivity studies have established that anxiety-like behavior relies on an abnormal functioning of a network comprising basolateral amygdala (BLA), medial prefrontal cortex (mPFC), and ventral hippocampus (vHipp) [1]. For instance, in mice KO for the SERT 5-HT transporter, synchronization between the BLA and the mPFC has been described in the theta range during fear expression [2]. However, the previous studies do not shed light on the causal hierarchies in the flow of information in this network. For instance, the BLA-mPFC subnetwork could be responsible of initiating the anxious response, while the vHipp-mPFC subnetwork could respond to BLA-mPFC activation, being involved more specifically to “anxiety-triggered” behavioral inhibition.

To this aim, we are determining the existence of local and long-range transference of information in the BLA-vHipp-mPFC network, in SERT KO and wild type mice challenged to anxiety-triggering experimental protocols, and using in vivo multiple brain region electrophysiological recordings. In our experiments, fourteen adult male SERT KO mice along their wild type littermates were used, from whom we recorded the electrical activity in their home cages (spontaneous activity) and also while were subjected to two different behavioral tests for anxiety: Open Field (OF) and zero-maze.

Our results show that SERT KO mice display, in the home cage condition, increased baseline 4Hz cross-area spectral coherence between BLA and mPFC, but not between vHipp and mPFC, as compared to control mice. In addition, SERT KO mice display increased baseline BLA theta activity in the periphery of the OF, and decreased theta activation in mPFC and BLA when enter the center of the OF, as compared to wild type. We are currently investigating the spikes/LFP synchrony between the above mentioned structures, and using transfer entropy to determine whether there exist causal hierarchies in the flow of information in this network. Our work hopes to be a substantial contribution to the understanding of the informational neurodynamics involved both in normal and pathological brain functioning.

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42) Natural Modulations of Decision-Making: Dopamine Beyond Reward Effects within the Basal Ganglia

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While there is a vast literature describing midbrain dopamine (mDA) neural activity as a common brain signal for informing prediction error, this reward-based evaluation only takes into account phasic variations in dopaminergic neurons, leaving behind any functional effect from basal or tonic mDA neural activity. The mDA phasic variations determine the magnitude, and direction, of plasticity in corticostriatal synapses through positive reinforcement processes. This reinforcement changes lead to competitive interactions at cortico-basal ganglia circuits, compounding an essential process that gives shape to an action-selection mechanism based in maximizing expected rewards. As reinforcement learning (RL) in artificial intelligence has a well-described mathematical framework, the functional descriptions of mDA neurons are usually modeled as the computation of prediction errors following an RL architecture, modifying corticostriatal synaptic connections. RL models are capable of reproducing stimulus-action, action-reward, and stimulus-reward associations, in coherence with neuroscientific reports, indicating the relevance of DA setting these associations. Concerning the tonic activity in mDA neurons, recent works associate mDA tonic level with the exploration/exploitation ratio of a performing agent (i.e., how much the animal selects an option known as worst, evaluating changes in contingency). The description of a smart mechanism for regulating this ratio, fundamental while confronting decision-making tasks in variable environments, is an open scientific question for both, artificial intelligence and neuroscience. By taking the known neurophysiological effects of mDA neuronal activity in the corticostriatal connections, this work proposes a mathematical rate model of mDA neurons, which are located at the substantia nigra. The model proposed is an extension of a well-described model of two parallel cortico-basal ganglia circuits (cognitive and motor), which integrates the direct and hyper-direct loop in each of them. The model combines, in a single neural population, the tonic and phasic effects of mDA neurons, generating long-term depression, long-term potentiation, and continuous variations in corticostriatal connections. This integrative model is capable of confronting a reversal-learning while regulating the exploration/exploitation ratio.

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43) Effect of Spinal Cord Stimulation (SCS) in the nigrostriatal dopaminergic system of a α-synuclein model of Parkinson's disease

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Introduction. Parkinson's Disease (PD) is a neurodegenerative disorder characterized by the presence of progressive loss of dopaminergic neurons into substantia nigra (SN), and the present of Lewy bodies in these neurons. α-Synuclein (α-syn) is the main component of the Lewy bodies in sporadic cases of PD. Spinal Cord Stimulation (SCS), a neuromodulation technique consisting in the epidural delivery of electrical pulses in the dorsal portion of the spinal cord, has emerged as a potential treatment for the motor symptoms of PD. Evidence collected in pharmacological PD model, suggest that SCS could have long-term effects associated to neuroprotection. We study the possible neuroprotective effect of SCS that could be involved in the improvement of the motor performance of an α-syn animal model of PD. Material and Methods. Rats Sprague Dawley male was injected unilaterally in the SN with AAV6-α-syn. Thirty-two days after the viral injection, were treated with high-frequency (300 Hz) SCS for ten weeks, two sessions/week. We evaluated the motor performance by Stepping Test. By immunohistochemistry we evaluated the density of dopaminergic axons. Results. SCS prevents the motor alteration in Parkinsonian model and decrease the loss of dopaminergic axonal innervation in the dorsolateral striatum. Discussion. These results suggest that SCS might exert neuroprotective effects in the axonal innervation, phenomenon that contribute to alleviate the progression of motor symptoms in the α-syn animal model.

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44) Impact of Non-Invasive Spinal Cord Stimulation (NISCS) in a parkinsonian 6-OHDA rat model

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Spinal Cord Stimulation (SCS) has shown positive results for axial symptoms of Parkinson Disease (PD), advancing its potential use as a novel treatment option. Although SCS is an expensive and invasive surgical procedure. There are also associated risks such as infection and lead migration. This is the first study to-date to explore the effects of Non-Invasive Spinal Cord Stimulation (NISCS), a non-invasive technique that delivers current by electrodes located on the skin surface above the spinal cord at the thoracolumbar level. We used adult Sprague Dawley male rats with unilateral nigrostriatal dopaminergic lesions induced by the toxine 6-hydroxydopamine (6-OHDA), we evaluated the effectiveness of Non-Invasive Spinal Cord Stimulation (NISCS) by measuring the neural activity in the cortico-basal ganglia circuit and the motor function. For the first outcome, we compared the local field potential (before, during and after NISCS) from 5 different areas of the motor circuit, using the uninjured hemisphere as a control. For the second outcome, we evaluated the motor performance during 11 days of NISCS, using different behavioral tests. We compared the motor performance between the treated and non-treated (sham group) parkinsonian rats. NISCS was able to modulate the pathological neural activity and also motor function. Since this strategy is less expensive, safer, and easier to administer than other neuromodulation techniques, our findings might be relevant to the clinical practice.

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45) The impact of physical exercise on a model of Sprague Dawley rats with chronic stress in Parkinson´s disease

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Physical exercise has the ability to exert effects on cardiovascular, cerebrovascular and anti-inflammatory health. Studies show improvements in the quality of life in animals and in humans with neurodegenerative pathologies both in physical condition and motor performance: postural stability, balance and tremor in Parkinson´s disease. In addition, physical exercise has positive effects between stress and health problems in human. In this study, we analyzed the effects of physical exercise in a Parkinson 6-OHDA model in stressed rats. The animals were trained to perform physical exercise and underwent a movement restriction chamber as a stress model.

Different test were analyzed: Elevated body swing test, horizontal bar walking test and gait. In summary, ours results indicated that physical exercise works as a neuroprotective therapy, improves the motor capacity of animals with PD under chronic stress and could be a good strategy of future studies to exert effects potentially beneficial effects on PD in humans. Key words: physical exercise, Parkinson’s disease, motor signs, stress, 6-OHDA, animal model.

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46) Ventral Tegmental Area Dopaminergic Neurons Somatodendritic Tree Inputs Distribution: Relationships with Electrophysiological Activity

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In this study, our aim was to understand how the number and distribution of synaptic contacts correlates with spontaneous or driven (by aversive somatosensory stimulation) activity of ventral tegmental area (VTA) dopamine neurons, a population involved in motivated behavior and preference formation.

In urethane anesthetized mice, extracellular recordings and subsequent neurobiotin labelling of 12 single VTA neurons were performed. Dopaminergic phenotype was immunohistochemically confirmed, the entire somatodendritic domain was acquired under confocal microscopy, and a 3D reconstruction of each neuron was generated with *Neurolucida*. The presence of glutamatergic or GABAergic postsynaptic puncta (PSP) onto the recorded neurons was determined by double immunolabelling for neurobiotin and specific postsynaptic density markers. The number of contacts was estimated with the optical fractionator method and the distribution analyzed on the 3D reconstructions. Regarding PSP distribution we found a trend for inhibitory PSP to locate in lower order dendrites (Mann-Whitney, $p = 0.063$) and a statistically significant higher density of excitatory PSP in distal dendrites (Mann-Whitney,$p= 0.024$).

Electrophysiologically, we found a wide range of values in spontaneous activity variables such as frequency, coefficient of variation (CV) or bursting activity, consistent with previous reports. Yet, we found that none of these variables related to overall PSP number, density or distribution. After analyzing aversive stimulus driven responses, we found that 8 neurons were inhibited, 3 were activated and 1 was unresponsive. Also, we found no significant differences in the total number, density or distribution of excitatory or inhibitory PSP between these groups. However, when considering only the group of inhibited neurons, we found that those with a higher density of inhibitory PSPs had a more pronounced inhibition in response to the aversive stimulus (Pearson correlation, $r2 = 0.57$, $p= 0.049$). These data confirm the existence of neuronal subpopulations in the VTA in relation to aversive stimulus coding, but question whether those responses (inhibition, activation) relate to electrophysiological parameters (frequency, CV, bursting activity). On the other hand, however, our data does support the idea that differences in responses might ultimately relate to differences in organization of synaptic inputs onto individual neurons.

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47) Effect of Astrocytes Photo-activation on Remyelination in Freely Moving Mice

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Demyelinating diseases, such as multiple sclerosis (MS), are characterized by the loss of myelin in several regions of the central nervous system (CNS), where myelin is synthesized by the oligodendrocytes (OLs). After a demyelinated insult, there is a spontaneous remyelination process (i.e. myelin repair) characterized by the migration, proliferation, and differentiation of oligodendrocyte precursors (OPCs). In addition to this response of the oligodendroglia population, a highly conserved characteristic of demyelinated areas is the massive recruitment of reactive astrocytes. These glial cells can modify oligodendroglia dynamics and function by releasing several molecules such as cytokines, chemokines and growth factors potentially affecting production of newly formed oligodendrocytes and in turn myelin synthesis and repair. Evidence has pointed out a role for astrocytes in the demyelination/remyelination proccess but the precise contribution and the subcellular mechanisms are not completely understood. To study the role of astrocyte activity on remyelination, we use the lysolecithin (LPC)-induced demyelinated lesions model in the mouse corpus callosum (CC). Thirty days before injecting LPC into the CC, astrocytes are infected with a AAV-GFAP-ChR2-mCherry adenovirus. This construct induces the expression of the channelrhodopsin 2 (ChR2) photosensitive ion channel specifically in astrocytes. To confirm the photoactivation of ChR2-expressing astrocytes, we performed intracellular calcium imaging of astrocytes during light stimulation, as well as electrophysiological recordings aimed to follow astrocyte membrane potential during photostimulation by performing patch clamp recordings in the conventional whole cell configuration (I=0, voltage follower mode). After LPC-stereotaxic injection we accomodate -in the same surgery-, a mini-optic fiber just upon the lesioned area. This paradigm allow us to photostimulate astrocytes present in the demyelinated lesion in freely moving mice at different time points after the onset of demyelination. LPC-injected mice were photo-stimulated in everyday sesions during one week, either from 7 to 14 days post LPC-injection (dpi) or from 14 to 21 dpi. We are currently analyzing the number of OPCs and OLs as well as the myelin content of the demyelinated lesions at different time points of the remyelination process by performing immunohistochemistry and confocal microscopy on post morte sections. This project will contribute to understand the astrocyte-oligodendroglia interaction underlying the progression of the remyelination in demyelinated diseases such as MS.

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48) Focal Demyelination in the Cerebellum: a Preclinical Model for the Study of Multiple Sclerosis

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Multiple Sclerosis (MS) is a demyelinating disease characterized by the loss of myelin in the central nervous system (CNS). Since myelin allows for the proper communication of the nervous system, MS patients show several neurological impairments such as motor, locomotor and respiratory disorders, which represent highly prevalent symptoms. In our laboratory we have implemented an in vivo model of demyelination /remyelination which closely resembles the cellular dynamics present in MS demyelinating lesions. This paradigm is based on the induction of demyelinating lesions by the injection of lysolecithin (LPC), a toxin that kills oligodendrocytes (myelin forming cells of the CNS) specifically. The main advantages of this particular model of MS-lesions is that recapitulates the cellular migration, proliferation and differentiation that occur during the spontaneous remyelination (i.e. myelin repair) in a well-defined and highly stereotyped time course: from 0-7 days post LPC injection (dpi) oligodendrocyte precursors (OP) proliferate and migrate into the lesion, between 7-14 dpi OPs differentiate to mature oligodendrocytes that in turn remyelinate axons from 14 to 30 dpi. By using this toxin-induced demyelinating lesion paradigm, our aim was to develop a MS murine model that reproduce some relevant clinical hallmarks of MS in order to study the cellular mechanisms underlying disease progression. We injected LPC into the cerebellar white matter by using an stereotaxic apparatus (antero-posterior +1.7 mm, medio-lateral +/- 1.5 mm, dorso-ventral -1.7 mm relative to lambda) and then we performed a rotarod treadmill test at 7, 14 and 21 dpi to evaluate balance and motor coordination of LPC-lesioned mice. In parallel, unrestrained whole-body plethysmography was performed in order to study breathing stability and ventilatory function in the same animals. Our results showed that LPC-injected mice displayed irregular breathing at rest, a reduced response to hypercapnia along with a decreased central chemoreflex function. Rotarod treadmill test results showed that both total distance and time on the rotating bar were reduced after LPC-induced lesion compared to control baseline (before the LPC-injection). Interestingly, a partial recovery is observed in these locomotor parameters from 7 to 21 dpi. Our results support that cerebellar white matter LCP-lesioned mice may be a clinically relevant MS model to study locomotor performance and respiratory function.

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49) Altered processing of odor-objects in a mouse model of Fragile X Syndrome

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One of the most prevalent symptoms in individuals with Fragile X syndrome (FXS) is an altered sensitivity to sensory stimuli. It has been suggested that the abnormal social behavior in FXS might be secondary to inappropriate filtering to daily life stimulus. Yet, compared to cognitive and social functioning, how sensory information is processed in FXS has been largely understudied. Here, we use a combination of behavioral and *in vivo* electrophysiological tools to study the neurophysiological alterations underlying aberrant sensory processing in the olfactory system of the FXS mouse model (*Fmr1*-KO). Olfactory information is integrated and ultimately decoded by a unique ensemble of pyramidal neurons (Pyr) in the olfactory cortex (OC).The OC is an auto associative neuronal network, capable of storing and recalling odor-objects even though there are some features of the sensory stimulus missing, a process leading to perceptual stability. Depending on the context, however, pyramidal neurons in the OC decorrelate partially overlapping patterns of Pyr activation and treat them as different, a process called pattern separation. Using a go-no go behavioral task we have found that *Fmr1*-KO learn to discriminate between a rewarded and a not rewarded odorant, but cannot morphed very similar mixtures to promote pattern separation. In addition, we have preliminary data showing that *Fmr1*-KO exhibit altered olfactory sensitivity and a hyperexcited olfactory cortical network. Altogether, our results suggest that *Fmr1*-KO create inappropriate olfactory representations partially relying on dysfunctional cortical processing.

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50) Sensory processing alterations in the olfactory cortex of a Fragile X Syndrome mouse model

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Fragile X Syndrome is the most prevalent form of monogenetic-caused autism. Individuals with this condition exhibit difficulties engaging in normal day-to-day tasks due to cognitive and sensory disabilities. Investigations using non-human models like *Fmr1*-KO mice indicate a diverse spectrum of molecular, synaptic and physiological alterations that could relate to behavioral impairments. Particularly, it has been shown that *Fmr1*-KO exhibit problems in odor sensitivity, discrimination and odor-mediated learning processes. However, how the olfactory cortex process olfactory information leading to behavioral alterations is not known. Here, we performed extracellular recordings in the olfactory cortex of awake and freely-moving mice (*Fmr1*-KO and wild-type) while odors were passively and consecutively presented in a 19 by 30 cm arena. Recordings of 16 electrodes implanted at their piriform cortex were analyzed by off-line clustering analysis and the periods the animal spent sniffing during odor presentation quantified. Our preliminary results show that, during vehicle and low-concentration (D-limonene 0.1 ppm) odor presentations, *Fmr1*-KO sniffed a greater amount of times compared to control, a pattern inverted during presentations of social (opposite-sex bedding) and high-concentration (D-limonene 10 ppm) odors, suggesting that odor-sampling is altered in the KO. Interestingly, we found that the cortical neurons of *Fmr1*-KO exhibit a higher basal firing rate compared to control as well as in the increase in firing rate observed after odor presentation, more significantly during female bedding presentation. We hypothesize that problems associated with stimuli discrimination and sensory processing may be due to hyperexcitability of cortical neurons, affecting the neural network's dynamics of odor perception.

51) Burrowing a Sensitive Test for Hippocampal Aging State in *Octodon degus*?

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Octodon degus (degus) can live between 8–10 years, under laboratory conditions, being useful in longitudinal studies. Many behavioral tests have been used to evaluate spatial or recognition memory, related to the hippocampal state. However, those tests have been developed and applied to rats and mice. Here we evaluate degus burrowing performance (BP) and compare it with their hippocampal physiological state during aging. We compared BP with the classic novel object recognition (NOR) test. Degus BT, from 25 to 71 months old, was measured, and we did not find a correlation between BT and aging (Pearson correlation r=-0.06; P value=0.8). However, from degus BP, we obtain a good separation between Good (GB) (n=11) and Bad Burrowers (BB) (n=14). BB criteria where set for an individual with less than 10% burrow food (150g). Degus performance was GB = 741 + 90 g and BB = 21 + 11 g, with a significance difference $p<0.0001$. With the NOR test, no difference found for our degu's population, having a homogenous distribution (NOR preference index (PI) = 63.9 + 2.4). To evaluate the hippocampal network state, we have used a 252 multielectrode array (MEA). We computed the firing rate (FR), inter-spike interval (ISI) before and after adding GABAa antagonist receptor picrotoxin (PTX). Moreover, two separated hippocampal populations Interneuron (Int) and pyramidal cells (Pyr) were analyzed separately. In a preliminary result, we find a difference from Int and Pyr population. BB had 56.3% Int and 43.7% Pyr, while GB show 67% Int and 33% Pyr. Respect to FR and ISI, BB present a decrease of FR activity compared to GB, both before PTX (BB: 0.6 + 0.04 Hz vs GB: 1.2 + 0.3 Hz) and after PTX (BB: 1.1 + 0.1 Hz vs GB: 1.7 + 0.4 Hz). While ISI, BB show a decrease values than GB, both before PTX (BB: 3.2 + 0.1 ms vs GB: 5.8 + 1.3 ms) and after PTX (BB: 1.1 + 0.1 ms vs GB: 1.5 + 0.5 ms). The results suggested that BT and hippocampal physiology are good potential biomarkers to understand the mechanisms underlying aging further.
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52) Endocannabinoid Signaling Regulates Inhibition From Somatostatin-expressing Gabaergic Neurons In The Prefrontal Cortex

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Endocannabinoids (eCBs) are potent modulators of synaptic function throughout the central nervous system (CNS) and alterations in this neuromodulatory system are observed in several neuropsychiatric disorders, prompting the suggestion that it modulates emotional and cognitive processes in associative areas such as the prefrontal cortex (PFC). However, the specific neural circuits and cell types participating in eCB signaling in the PFC are not well understood. Given the importance of synaptic inhibition in shaping neural activity, we study eCB modulation of GABAergic synapses from somatostatin-expressing interneurons (SOM-INs), a major population of inhibitory cells in the PFC. By targeting dendritic regions of pyramidal cells where excitatory synapses congregate, SOM-INs regulates synaptic integration and plasticity to influence principal cell output. Using optogenetic tools to selectively activate SOM-INs in whole-cell patch experiments, we found that postsynaptic inhibitory currents mediated by SOM-INs (SOM-IPSCs) in cortical pyramidal cells are sensitive to WIN 55,212-2, a potent CB1R agonist, in control mice but not in mice lacking CB1Rs in SOM-INs (SOM-CB1R KOs). Moreover, theta-burst stimulation triggered a long-term depression of SOM-IPSCs (TBS-iLTD) that is absent when CB1Rs are blocked by the selective antagonist AM251. Given that CB1Rs profoundly shape inhibitory synapses from SOM-INs, we further evaluated the impact of their removal in SOM-INs. In voltage-clamp experiments, input-output curves of electrically evoked IPSCs revealed an upregulation of GABAergic inhibition in SOM-CB1 KOs compared to littermate controls. In addition, evoked IPSCs showed stronger paired pulse depression, suggesting an enhancement of GABA release probability. Finally, we found that transient application of 5-HT, another widespread neuromodulator, also persistently depressed SOM-IPSCs that is dependent on CB1R activation. Our result strongly suggest an intimate interaction between the 5-HT and eCB systems in regulating inhibitory activity of SOM-INs in the PFC. We are currently determining how 5-HT signaling alters eCB-dependent plasticity such as TBS-iLTD and depolarization induced suppression of inhibition (DSI). Altogether, our results demonstrate the ability of eCBs and 5-HT to coordinate their actions to control GABAergic inhibition from SOM-INs and thereby modulate information flow from sources such as the thalamus, hippocampus and amygdala to shape associative cognitive processing in complex ways.

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53) Study of LbCLC-A and LbCLC-B putative proteins expressed in Leishmania braziliensis opens a new path for understanding the function and role of the CLC exchanger CLC-6 in neuropathies

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The CLC protein family of Cl- channels and Cl-/H+ exchangers is ubiquitously expressed in many branches of life. It performs diverse functions of physiological relevance, including maintenance of resting membrane potential in skeletal muscle, and Cl- shunts or pumps to support osmolar and pH regulation. In neurons, CLC-3 has been reported as a regulator of postsynaptic membranes excitability, additionally, the disruption of CLC-6 has been associated with neurodegeneration, specifically in NCL

To understand the role that CLC plays in neurons and complement our knowledge about its physiological role, we transfected Chinese Hamster Ovary (CHO) cells with two expression plasmids that contained the gens of the putative proteins LbCLC_0210(CLC-A) and LbCLC_3670 (CLC-B) of L braziliensis that are closely related to CLC-6 in base of its nucleotide sequence. Two cell lines resistant to geneticin were generated, and whole-cell recordings with patch-clamp were obtained with CHO cells that heterologously express the putative proteins, proved by immunodetection. Preliminary results show that LbCLC-A show significantly different responses to depolarizing and hyperpolarized potentials with currents 1,5 folds higher in contrast to Wt cells, interestingly the reversal potential of CLC-A CHO cells changes toward more positive voltages (n=5) which is unexpected according to the stoichiometric CLC exchanger that mobilize one negative net charge inwards the cell. Instead, LbCLC-B shows significantly different responses to hyperpolarizing potentials with currents 2 fold higher in contrast to Wt cells (n=9). Furthermore, lbCLC-B shows no change in its reversal potential (-9mV) nor response to either acid or alkaline conditions (n=5), although the unresponsiveness of CLC-B to changes in pH fits the findings that the absence of CLC-6 does not change intracellular compartments pH in neurons. Together these results suggest that intracellular CLC exchanger functions mainly by sensing intracellular compartments voltage changes, disruption in this sensing process could contribute to lysosomals products accumulation in NCL. It also opens the possibility of using Leishmania as a prokaryotic model for the CLC study. Funding by Colciencias, & Universidad Nacional de Colombia.

Colciencias; Departamento de Biologia, Universidad Nacional de Colombia

54) Protein kinase C activation modulates TRPM8 function in cold thermoreceptor neurons

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TRPM8 is the main molecular entity responsible for detection of cold temperatures in the somatosensory system. This Ca^{2+}-permeable cation channel is activated by cold, cooling compounds such as menthol, and voltage. It has been suggested that TRPM8 function could be regulated by the activity of Protein Kinase C (PKC). To further explore this modulation, we assessed recombinant channel function using patch-clamp recordings and Ca^{2+}-imaging in HEK293 cells, and native channel using Ca^{2+}-imaging in cultured trigeminal neurons and extracellular recordings in corneal free nerve endings of cold thermoreceptors. Since the release of bradykinin activates Gq-coupled receptors and PKC in inflammatory conditions, in this study we used both bradykinin, and phorbol esters such as phorbol myristate acetate (PMA), to activate PKC. In addition, we used mass spectrometry, to identify residues where a putative PKC-dependent phosphorylation occurs. Functional evaluation of TRPM8 after PKC activation with PMA shows an important reduction of the maximal response of TRPM8 to cold and menthol, causing a shift in the temperature threshold activation to lower temperatures, in both trigeminal neurons and TRPM8-expressing HEK293 cells. In agreement with these results, we found that in corneal TRPM8(+) cold thermoreceptors, PMA also induces a reduction of the ongoing activity and maximal cold-evoked responses. Noise analysis revealed that the effect of PKC activation on TRPM8 function is mainly explained by a reduction in the number of active channels at the plasma membrane. Finally, we also found that the activation of PKC allows the recruitment of at least one new phosphorylation site, within the N-terminal domain. Mutation of this residue partially reduces the PKC-mediated down regulation, suggesting that this phosphorylation could play an important role in this modulation. Altogether, these results indicate that PKC acts as a negative modulator of TRPM8 channels, suggesting a relevant role of this kinase in cold sensing in inflammatory conditions.

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55) Basal Phosphorylation modulates TRPM8 channel function

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TRPM8 is a member of the transient receptor potential (TRP) ion channel family, which is expressed in sensory neurons and is activated by cold and cooling compounds, such as menthol. This channel is the major molecular entity underlying cold transduction machinery in cold thermoreceptor neurons of the somatosensory system. It has been suggested that TRPM8 function could be regulated by several kinases that phosphorylate the channel in basal conditions. However, despite the central role of TRPM8 in cold sensing, the contribution of this critical post-translational modification (PTM) to the TRPM8 channel function under physiological conditions is still poorly understood. To explore the mechanism underlying this regulation, we studied the phosphorylation state in basal conditions by using mass spectrometry analysis of immunoprecipitated TRPM8 channels. Using this strategy, we identified four phosphorylated serines within the N-terminal domain. Functional evaluation of TRPM8 unphosphorylated mutants of these residues using Ca^{2+}-imaging and patch-clamp recordings revealed a significant increase in cold- and menthol-evoked responses compared to wild type channels linked to one of these residues. This enhancement in TRPM8 function is similar to the one observed after inhibition of the basal tone of kinase activity using staurosporine. The increase in TRPM8 responses induced by this protein kinase inhibitor is associated to a shift in the $V_{1/2}$ towards more negative membrane potential and an increase in the g_{max} value. Altogether, these results indicate that basal kinase activity acts as a negative modulator of TRPM8 function, and suggest that constitutively phosphorylated residues within the N-terminal domain of TRPM8 tune the cold- and menthol-sensitivity of this polymodal thermo-TRP channel. Our results shed light on the molecular bases of the regulation of TRPM8 by this PTM, clarifying its role as a physiologically relevant, dynamic and reversible form of functional regulation of this cold-sensitive TRP channel.

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56) A CAN channel that modulates neuronal firing

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Neuronal excitability is regulated by several conductance present in the membrane surface, they respond dynamically to synaptic stimuli. Neurons segregate and relocates channels to maintain a target level of excitability. In this regard, neurons treated with tetrodotoxin (Na+ channels blockade), increases their excitatory postsynaptic current by upregulating postsynaptic glutamate receptors, thus keeping the level of excitability. Moreover, experiments in hippocampal pyramidal neurons, depolarizing stimuli induce a relocation of potassium channels from small puncta to a widespread somatic distribution which reduce their excitability. In this work, we evaluated the participation of a *C*alcium-*A*ctivated *N*on-selective (CAN) cation channel TRPM4 in the cortical pyramidal neuron excitability and the effect of their inhibition in the increase in excitability induced by cholinergic transmission. We use a pharmacological approach with 9-Phenanthrol and 4-Chloro-2-[[2-(2-chlorophenoxy)acetyl]amino]benzoic acid (CBA) and analyzed the response on cortical primary neuronal cultures (DIV14-21) treated with Carbachol (Cch, non-hydrolysable analogue of acetylcholine) in terms of membrane potential and spontaneous synaptic transmission. We found that both inhibitors reduce spontaneous synaptic transmission and reduce the action potential dependent synaptic transmission in non-stimulated conditions, moreover, we found that CBA reversibly depolarizes pyramidal neurons and reduce spontaneous neuronal firing. In neurons stimulated with Cch, we observed that both inhibitors reduce neuronal firing induced by Cch. Altogether, our results suggest that TRPM4 play an important role in the modulation of neuronal excitability.

FONDECYT 1181814 FONDECYT 11180536

57) Regulation of neuritogenesis progression by a CAN channel

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Neuritogenesis is a critical process where neurons generate and growth processes which then turns in to dendrites or axons. Neuritogenesis progresses in 5 steps in which neurons increases the number and size of their projections. This process is controlled by the actin cytoskeleton through posttranslational modification and changes in the intracellular calcium, in this regard, filopodia formation experiments performed in absence of Ca2+i showed that neurite progression is arrested at initial stages. Moreover, it has been demonstrated that neurite elongation and neuronal development is affected by the activation of ion channels that regulates Ca2+i levels. CAN channels are non-selective monovalent cation conducting channel activated by Ca2+i, which modulates intracellular calcium in several cellular types including neurons. In this work, we assess the participation of TRPM4 a CAN channel in the neuritogenesis progress and the Ca2+i dynamics during early stages of neurite development. Using a combination of pharmacological modulation and genetic suppression of TRPM4 in a model of cortical neurons in culture, we performed multiplex immunofluorescence using cytoskeleton markers such as MAP2 (microtubules) and phalloidin (actin) and then, we characterized the neurite initiation and measure the neurite number and length during neuritogenesis. Additionally, we assessed the Ca2+ dynamics during the first stages of neuritogenesis using Fluo-4 calcium probes. We found that pharmacological inhibition of TRPM4 change neurite length and number, thus affecting the stage progression. These results were similar to the effects observed with TRPM4 silencing using an shRNA. Current efforts are focused in the understanding of the actin dynamics and its relationship with changes in Ca2+i. These results bring insight in the role of TRPM4 as an indirect modulator of the cytoskeleton dynamics through the regulation of the intracellular calcium.

FONDECYT 1181814, FONDECYT 11180536

58) Presynaptic BK channels mediate long-term depression in the hippocampus

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BK channels are expressed in synaptic terminals where they have been shown to tightly control transmitter release by shortening the duration of presynaptic action potentials. However, the functional relevance of presynaptic BK channels in activity-dependent changes of synaptic strength is not well established. Here, using electrophysiological and pharmacological approaches, we report that low-frequency (5 Hz for 3 min) stimulation (LFS) of Schaffer collaterals triggers long term depression (LTD) at CA3–CA1 synapses in hippocampal slices from P4–P10 mice that is induced via the production of 12-(s)-HPETE, an arachidonic acid metabolite, that subsequently activates presynaptic BK channels. This LTD was mimicked and occluded by direct application of 12-(s)-HPETE (100 nM, 10 min). Both forms of LTD are presynaptic, as both the paired-pulse ratio (PPR) and the coefficient of variation (CV) were increased after the induction protocol. Interestingly, LFS-LTD and 12-(s)-HPETE-LTD were eliminated in the presence of paxilline but not iberiotoxin, suggesting the specific involvement of BK channels formed by a and β4 subunits. Consistent with this idea, in cell expression systems, the addition of 12-(s)-HPETE does not change the electrophysiological properties of the BK channel when the α subunit is expressed alone, but strongly increases the channel open probability of (a + β4) BK channels. Moreover, we found that BK channels are only required during induction, but not during maintenance as paxilline failed to reverse LFS-LTD when applied 10 min after LFS. In agreement with previous reports, application of the selective group I mGluR agonist DHPG for 10 min also induced a chemical LTD that included an increase in PPR and CV and was occluded by 12-(s)-HPETE. We further show that DHPG-LTD was prevented by paxilline but not iberiotoxin. Thus, DHPG-LTD also requires the activation of (a + β4)BK channels. Our findings reveal a previously unknown link between 12-(s)-HPETE and BK-mediated regulation of synaptic strength at central synapses and highlight a role of BK function in LTD, which may have a role in cognitive processes such as learning and memory.

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59) TRPV1 channel activation recovers decreased hippocampal synaptic plasticity in a model of Attention Deficit Disorder and Hyperactivity induced by prenatal exposure to nicotine

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Attention Deficit Hyperactivity Disorder (ADHD) is a neurobiological disorder characterized by symptoms of hyperactivity, impulsivity and inattention. Despite its high prevalence in the population, the molecular and neurophysiological bases of the disorder are still poorly known. An important structure that has been associated with ADHD is the hippocampus, which is the structure where the most accepted synaptic plasticity models of how information is stored in the brain have been studied. In this context, TRPV1 channels have been related to hippocampal synaptic plasticity models, since their activation by Capsaicin is able to facilitate LTP. In our laboratory we have been implemented a murine model of ADHD induced by prenatal exposure to nicotine (PNE). This model, in addition to presenting the disorder phenotype, shows a decreased LTP in *stratum radiatum* of the CA1 area. Using electrophysiological approaches, we investigated the effect of activation of TRPV1 channel on TBS-dependent LTP in CA3-CA1 synapses of hippocampus. Our results show that PNE mice have a reduced LTP compared to controls (No PNE): from 155,1±0,9% n=4,6; to 129,0±0,6% n=4,5. This impaired LTP was not observed when slices were treated with 1mM of Capsaicin (PNE_{Cap}=149,9±1,4; n=3,5). This results shows for the first time that activation of TRPV1 reestablish the reduced LTP observed in a model of Attention Deficit Disorder and Hyperactivity induced by prenatal exposure to nicotine. Nevertheless, the cellular and molecular mechanisms involved in these synaptic mechanisms are still unknown.

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60) Atomoxetine reestablishes long term potentiation in a mouse model of ADHD

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Attention Deficit/Hyperactivity Disorder (ADHD) is the most prevalent psychiatric childhood disorder, characterized by hyperactivity, impulsivity and impaired attention, treated most frequently with methylphenidate (MPH). For children and adults with ADHD who do not respond satisfactorily or do not tolerate well stimulants such as MPH or D-Amphetamine, for them the alternative is to use Atomoxetine (ATX), a norepinephrine (NE) transporter inhibitor that increase extracellular NE. We examined the effects of ATX on behavior and hippocampal synaptic plasticity in the murine prenatal nicotine exposure (PNE) model of ADHD. ADHD symptoms were measured using behavioral tests, open field for hyperactivity and the Y-maze for spatial working memory. Further, ATX effects on long-term potentiation (LTP) in hippocampal slices at the CA3-CA1 synapse were assessed. PNE mice exhibited the behavioral deficits of ADHD, hyperactivity and spatial memory impairment. Intraperitoneal injection of ATX (2 mg/kg/day) restored these behaviors significantly after 7 days. In PNE mice hippocampal LTP was reduced (110.6 ± 4.5% %; n=7) compared to controls (148.9 ± 5.2%; n=7; $p<0.05$). ATX administration (5 µM) reestablished the LTP in PNE mice to levels similar to the controls (157.7 ± 6.3%; n=7). Paired-pulse ratios (PPR) were not significantly different for any condition. These results indicate that administration of ATX in a PNE model of ADHD reestablishes TBS-dependent LTP in CA3-CA1 synapses. The results suggest postsynaptic changes in synaptic plasticity as part of the mechanisms that underlie improvement of ADHD symptoms induced by ATX.

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61) Role of the somatostatinergic inhibitory neurotransmission on excitatory synapses of the dentate gyrus during aging

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Introduction:Aging is characterized by cognitive decline associated with a decreased capacity to build new memories. During aging, the finely tuned balance between excitatory and inhibitory neurotransmission becomes disturbed, affecting neuronal networks in brain structures critically involved in learning and memory, such as prefrontal cortex and hippocampus. In the hippocampus, especially in the dentate gyrus (DG), the synaptic connections between inhibitory interneurons (INs, association neuron which mediates synaptic inhibition by secreting the inhibitory neurotransmitter g-aminobutyric acid -GABA) and excitatory granule cells (GCs, neuron which mediates synaptic stimulation by secreting the excitatory neurotransmitter glutamate) participate in the episodic memory encoding and recall. In the hilus of DG approximately, 55 % of GABAergic INs express somatostatin (SST), a neuropeptide co-released with GABA to control the excitability of this network.. Inhibitory neurotransmission, and specially SST expression is diminished during aging. However, the correlation between the reduction of the SST-INs and the cognitive decline during aging remains unknown, and strategies to improve cognitive deficits in aging are scarce. We proposed a specific correlation between the reduction of inhibition exerted by SST-INs on GC, and the cognitive dysfunction observed in aged mice. Therefore, our working hypothesis is, the reduction of hilar somatostatinergic interneurons in the dentate gyrus is associated to impaired cognitive function in aged mice. Results:To test this hypothesis young and aged mice (6-24 months old) will be selected for analyses: The selected mice were fixed and the brain were isolated to measured the levels of expression of SST/GABA neurotransmission by immunofluorescence. In addition, morphological analysis of the dendritic architecture of GC and spine morphologies of GCs and/or SST in GFP visualized neurons. For this, we performed stereotaxic injection in the DG of AAV-GFP. Confocal images obtained of aged mice were analyzed. Discussion: The morphological changes, atrophy or diminish in dendritic spines were be associated to synaptic disfunction. Moreover, we showed a reduction in the expression of components of inhibitory neurotransmission (GABA and SST) being compatible with the loss of inhibition exerted by SST-INs on GC and cognitive impairment in aging.

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62) Pannexin1: a “brake” for actin remodeling and structural synaptic plasticity in hippocampal neurons

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Neurons are highly specialized cells whose polarized morphology allows them to process information within the brain. The highly branched and complex morphology of their dendritic tree is crucial to establish contacts and neural circuits. Rearrangements of the neuronal architecture accompany the modifications in the synaptic functionality that lead to synaptic plasticity (SP). This latter is manifested as long-lasting changes in the synaptic strength that is been widely pointed as the molecular basis of learning and memory. In fact, long-term-potentiation (LTP) and long-term-depression (LTD) of the synaptic efficacy are the most prominent forms of SP and the mechanisms governing their induction have been proposed to be finely tuned during experience-induced neuronal activity, as well as during central nervous system development and upon neuropathological conditions. Previously we demonstrated that Pannexin 1 (Panx1), a non-selective membrane channel, modulates the induction of excitatory SP by preventing LTP and favoring LTD-mechanisms in hippocampal neurons. Here we show that the absence of Panx1 in knock-out mice (Panx1-KO) promotes the structural remodeling of neuronal architecture by favoring dendritic branching, spine maturation, spine-innervations and by increasing the size of the postsynaptic density (PSD) in hippocampal neurons. Consistently, modifications in the frequency of mEPSCs and in the number of functional synaptic contacts are also observed in Panx1-KO mice compared to wild-type littermates. These data strongly suggest a stabilizing role of Panx1 in neuronal morphology and structural SP. Remarkably these modifications are associated with increased expression of actin-related proteins and enhanced F-actin content in hippocampal tissue of Panx1-KO mice, suggesting that the role of Panx1 in neuronal morphology and structural SP relies on actin organization and dynamics.

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63) Role of Panx1 in metabotropic glutamate receptor type I synaptic plasticity in a mouse model of Alzheimer Disease

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Alzheimers disease (AD) is a chronic, progressive and irreversible neurodegenerative disease with clinical features of memory loss, dementia, and cognitive impairment. Although the pathophysiological mechanism is not fully understood, inflammation has been shown to play a critical role in the pathogenesis of AD. Inflammation in the central nervous system is characterized by the activation of glial cells and the release of proinflammatory cytokines and chemokines. On the other hand, βA oligomers (βAos) can affect synaptic plasticity by altering glutamate recycling at the synapse, reducing the size and number of dendritic spines and promoting long-term depression (LTD). Interestingly, this promotion of LTD is dependent on the activation of mGluR5. In addition, it is known that the activation of mGluRs causes the release of ATP and adenosine through Pannexin 1 channels, through calcium oscillations, modulating, in turn, the synaptic plasticity mediated by metabotropic glutamate receptors. This is why Pannexin 1 is proposed as a new therapeutic target, as it is an indirect regulator of extracellular levels of glutamate. Through the use of APP / SEN1 transgenic mice and the treatment with Probenecid, we intend to reverse the characteristic physiopathological characteristics of this disease through the performance of behavioral, immunohistochemical, biochemical and synaptic plasticity tests. We found an increased expression of Panx1 channels in hippocampal slices from Tg mice and an exacerbated Panx1 activity in response to glutamate receptors activation. Crucially, acute inhibition of Panx1 activity with PBN attenuates excitatory synaptic defects in the AD model. Indeed, PBN normalized long term potentiation and depression to levels comparable to those observed in wild type (Wt). These findings correlate with a decreased level of activated p38MAPK, as part of possible mechanisms underlying sAβos-induced synaptotoxicity.

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65) Effects of the topology of electrical synapses between inhibitory neurons on the activity patterns of a balanced network

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The effects of the electrical synapses on the dynamics of neural networks is being actively studied. Previously we showed that in networks with excitatory and inhibitory neurons, electrical synapses between excitatory type neurons can enrich the variety of network firing patterns. However, gap junctions in the cortex are mainly connecting inhibitory neurons between them. It is known that these connections increase the synchrony of the network by promoting oscillatory activity, but many studies with numerical simulations consider an all-to-all or a random coupling for electrical synapses, a biologically unrealistic situation. Given the physical contact necessary for the gap junction, it is most natural to connect only neighboring neurons with electrical synapses, in a lattice-style topology. We are studying whether the topology of the electrical connections between inhibitory neurons can have an impact on the network activity. For doing this, we simulate a neural network model with populations of 1000 excitatory and 250 inhibitory conductance-based neurons connected by chemical synapses, adding electrical synapses between the inhibitors in a random or lattice pattern. Our results indicate that with both topologies the connection of electrical synapses between inhibitory neurons promotes the synchrony of the network and the occurrence of repetitive activity, converting a network that was transiently synchronized, to a network that remains synchronized most of the time. In addition, under some conditions, the lattice topology network further promotes the occurrence of low frequency oscillations. Fondecyt Projects 1181076 (P.O.) and 3170342 (K.X.). PO is partially funded by the Advanced Center for Electrical and Electronic Engineering (FB0008 Conicyt, Chile). The Centro Interdisciplinario de Neurociencia de Valparaíso (CINV) is a Millennium Institute supported by the Millennium Scientific Initiative of the Ministerio de Economía (Chile).

66) Whole-brain model of 5HT2A-R neuromodulation reproduces predictions from the entropic brain hypothesis

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The "entropic brain" hypothesis proposes that the *richness of experience* reported during psychedelic experiences correlates with an increased brain signal diversity (i.e. *richness of signal*), which can be quantified via various methods of statistical signal processing, e.g. Shannons entropy. Besides the intrinsic scientific interest for study human consciousness, psychedelic drugs, since the 60s, have gathered a lot of attention from their clinical applications (and corresponding societal and economic benefits). Moreover, classic psychedelic drugs share a common molecular feature: their high affinity for the serotonin receptor 2A (5HT2A-R). In addition, simulation studies show a critical role of the distribution of 5HT2A-R on human brain for reproducing fMRI data recorded on humans treated with LSD. Together, this suggest that 5HT2A-R agonism concomitantly induces changes on the state of consciousness and increases the brain signal diversity.

However, current bioethical, experimental and political limitations regarding psychedelic research hinders the development of this field, forcing the researchers to use alternative approaches to understand the neural mechanisms involved on the psychedelic experience. Here, to by-pass the aforementioned limitations, we simulate human brain dynamics during resting state with and without 5HT2A-R agonism. In this work, we will study the changes in the Shannons entropy of simulated firing rates of brain regions under 5HT2A-R agonism. We aim to i) reproduce elemental predictions of the "entropic brain" hypothesis and ii) explain these changes based on the model parameters.

We found that, on average, 5HT2A-R agonism increases the Shannons entropy of brain regions. In addition, the node strength (a local feature of the structural connectivity) explains more than the 70% of the variance of the changes of entropy, while the density of 5HT2A-R explains less than 5%. This is consistent with the idea that the effect of neuromodulation is given mainly by a combination of connectome properties and the sepecific brain regions neurochemistry.

To our knowledge, this is the first work that test this hypothesis on a mathematical model and our results are in agreement with several studies finding that 5HT2A-R agonism increases brain entropy.
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67) Modularity and Small-Worldness enhance Multi-stable Dynamics in biophysical neural networks

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One remarkable property of the dynamics of resting-state brain fMRI and EEG/MEG recordings is the presence of multistability and metastability. These properties characterize “brain states” or activity attractors, which have been found in the absence of external stimuli. However, it is unclear how those brain states are created and sustained in time.

Multistability is thought to be an important mechanism for dealing with sensory novelty and to allow for efficient coding of information in an ever-changing surrounding environment. Many advances have been made to understand how connection delays, chaos, and noise contribute to build this dynamic. Little or no attention, however, has been paid to influences that network topology exerts to allow the switching between different network states.

For addressing the latter, we studied how network topology modifies the emergence of dynamical Functional Connectivity (dFC) in network models of biophysically inspired neurons.

For this, we simulated 250 Huber&Braun oscillatory neurons connected in different topologies: latticed, small-world and random. dFC was calculated by comparing the functional connectivity FC matrices that describe the pair-wise phase synchronization between the activity of two neurons. Quantification of brain states was done by PCA and clustering of FCs.

Our results show that when only the structure is considered (binarized network), multistability is better sustained in networks with Small-World topology than in random networks. Moreover, latticed networks support multistability even better when compared to Small-World topology. Additionally, densely connected networks achieve the maximum multistability at a lower global connectivity weight than sparse networks. Topological analysis suggests that the Modularity coefficient of the network is a predictor for the multistable behavior.

68) Noise improves the assessment of information directionality between weakly coupled neuronal networks

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Networks in the brain are analyzed from three perspectives: Structural Connectivity (anatomical connections), Functional Connectivity (statistical dependencies of the activity) and Effective Connectivity (EC; causal relationships). The main feature of EC is to assess the causal effects between network components, and this can be done with model-dependent (parametric) and model-free (non-parametric) methods. The later case extends the concept of Granger Causality and defines the concept of Information Flow as Transfer Entropy (TE). An outstanding question in Computational Neuroscience is how the information flow and its estimators can be affected by the chaotic and stochastic nature of neural dynamics. In this work, we determined TE between two unidirectionally, weakly connected oscillatory neural populations. The oscillatory nodes are either of chaotic or non-chaotic nature, and we systematically varied connectivity and noise parameters. Here, noise refers to the internal variability due to the stochastic behavior of ion channels. We use TE as a directed information measure between the average membrane potential of each oscillatory subnetwork. The standard TE estimation is based on Kraskov method (JIDT software) but the estimator becomes slow when data size is $>10^4$, so here we proposed a novel estimator based on Gaussian Copulas (GC) that reduces the computing time and also improves the estimation. In addition, several empirical techniques are used to describe the statistical dependencies, properties and dynamics of time series. Our main result indicates that noise decreases the information transfer between networks but, at the same time, improves the discrimination of directionality. The deterministic (noiseless) scenario shows higher information transfer but the estimators fail to predict the true directionality of transmission. The later effect is probably not a problem of the estimators but a consequence of the chaotic dynamical systems, that fall into an 'anticipated synchronization' regime. Keywords: Effective Connectivity, Transfer Entropy, Gaussian Copulas, Chaos, Noise.

69) Towards a Closed-loop Pattern-based Neurofeedback of Hippocampal Activity in Rats for Manipulating Spatial Memories

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The hippocampus plays a crucial role in memory consolidation and spatial navigation, which have been deeply studied thanks to its place cells' activity -that is, neurons that fire at specific locations in the environment. Moreover, it has also been shown that changes in place cell activity could also be highly informative about future trajectories of subjects when facing multiple choices. However, the role of this prospective activity in the actual execution of these choices has not been strictly elucidated. To address this issue, we designed a novel neurofeedback-based protocol that first aims to classify in real-time any specific dCA1 activity pattern that best account for the prospective encoding of spatial navigation during locomotor behavior. Our goal is to later use neurofeedback to finally manipulate these activity patterns in order to evaluate whether they also drive subject's behavior. Towards this end, we recorded dCA1 in rats performing a T-maze task and, by using machine learning techniques, we were able to successfully predict the future movement direction (left/right) solely from the hippocampal neural activity. Finally, we plan to design a closed-loop neurofeedback system to train rats to modulate their dCA1 activity patterns for a given movement direction and assess whether their activation consequently trigger the corresponding locomotor behavior.

70) Hippocampal Sharp-Wave Ripples and episodic memory onset along development

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Episodic memory relies on the ability of the hippocampus to process spatial information. This type of memory emerges late on postnatal lifetime, in correlation with hippocampal development. When this memory is build-up by using external/distal environmental cues is known as allocentric memory and, it is the latest form of episodic memory to emerge. Recently, it has been shown that allocentric memory is observed since postnatal day 18 (P18), but it is not fully developed until P38, when it reaches the adult-like form. However, it has been proposed that early reinforcement by allocentric task training could accelerate its adult-like expression. Although the mechanisms of memory formation remain unclear, research has pointed out sleep as a memory promoter and oscillatory electrical rhythms during sleep, such as cortical slow waves (< 1Hz), and hippocampal sharp-wave ripples (SWRs,100-250 Hz) as correlates of memory consolidation. With the aim to determine whether allocentric reinforcement could anticipate the maturation of episodic memory in parallel with changes in oscillatory activity, we performed an object-place task with or without reinforcement and *in vivo* LFPrecordings, throughout animal development, in the somatosensory and hippocampal cortices. Our results show that allocentric memory emerges around P32 (n=11, p=0.042), independently of early reinforcement and, changes in the power and density of sleep SWRs accompany the emergence of memory consolidation. Keywords: Neurosciences, Electrophysiology, Behavior, Development.

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71) Effect of sleep in the spatial representation system is related to successful performance in a spatial memory test

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The development in the study of place cells discovered by O'Keefe (1971) has put the focus on the study of spatial representation of the environment in the processes and functions lead by the hippocampus. Among these functions, the hippocampus plays a preponderant role in the establishment of spatial memory, in which sleep is fundamental, suggesting a possible relationship between sleep and the establishment of spatial representations by place cells. In this line, there is a query if sleep participates in the consolidation and configuration of spatial representations. One possibility is that sleep affects the configuration of place fields in a post-sleep exploration when place cells are reactivated during slow wave oscillations and are associated with Sharp Wave Ripples (SWR) in a post-learning sleep. In this study, we evaluate the influence of sleep on the variations in the configuration of a spatial map given by changes in spatial context during a spatial memory task. Specifically, we analyze the features of place cells recorded in hippocampal CA1 in terms of firing rate, place fields location and spatial correlation during object in place recognition (OPR) task and the reactivation and temporal coupling of place cell activity with the cortical slow wave oscillations and it correlation with the SWR during the post-learning sleep phase in adult Long Evans rats. Here we will present our results showing that post-learning sleep enhances performance in the OPR task. Also, we show that this is related with an enhancement of specific features as spatial correlation of place cells during the test and sharp wave ripples coactivation with these place cells during slow wave oscillations that allow to consolidate spatial patterns that are necessary for the spatial memory performance. The study of sleep`s influence on spatial representations given by place cells in the hippocampus will allow us to understand the importance of this process in the performance of a cognitive function such as memory.

72) Optogenetic stimulation of prefrontal cortex pyramidal neurons during acquisition of spatial-reference memory

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Location of relevant places in the environment (i.e. spatial-reference memory, SRM) is crucial for surviving. This memory is progressively acquired over repeated exploration of relatively stable environmental conditions.Throughout learning, subjects gradually improve their performance while implement strategies of increased efficiency to solving the task. Strategy implementation is a cognitive opertion supported by the prefrontal cortex (PFC), the associative cortex of the frontal lobe. We previously show in mice that pyramidal neurons in the medial-PFC (mPFC) increased firing during spatial memory acquisition, specifically when mice used the most efficient spatial strategy, which correlated to behavioral performance. Therefore, we hypothesize that prefrontal activation would improve performance and would increase the utilization of spatial strategy during acquisition of SRM. Therefore, we optogenecally stimulated prefrontal pyramidal neurons in freely-moving mice expressing ChR2 in the mPFC (strain: Thy1-ChR2-YFP) during the acquisition of SRM in the Barnes maze.We first established optimal laser illumination conditions to increase firing in the mPFC of Thy1-ChR2-YFP mice. We found that maximum firing was obtained at laser intensities of 1-2 mW. No increase of firing was found in WT mice at any tested laser intensity. Therefore, this illumination protocol was utilized for stimulation of mPFC during acquisition of SRM. Laser illumination was delivered to WT and Thy1-ChR2-YFP mice during all acquisition trials exclusively during the navigation phase. Consistently, firing rate was significantly increased during navigation in Thy1-ChR2-YFP mice compared to start and goal phases. In WT mice, laser illumination did not modified firing during any trial phase. At behavioral level, preliminary results show that laser illumination in the mPFC decreased escape latency and increased the utilization of spatial navigation strategy in Thy1-ChR2-YFP mice compared to WT during acquisition of SRM. These results suggest a critical role of prefrontal neural activity in cognitive functions as implementation of efficient spatial strategy during acquisition of SRM.

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73) A search for slow-wave sleep events enhancer stimulation pattern with neural field theory

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Memory consolidation is the biological process when the labile memories traces become stronger in neo-cortical networks and other substrates. The offline-brain stages are presumably the best time windows to promote memory consolidation due to the lack of input interference. Sleep occupies the third part of our lives and is the longest offline stage. Also, the occurrence of physiological events that characterize the NREM sleep stages, spindles for the N2 and slow-waves for the N3 stage, correlate with improvement in memory consolidation. In the last decade, many studies employed direct and sensory stimulation to enhance the occurrence of these events, and the results also show an increment of performance in declarative memory consolidation tasks. The characteristics of the stimulation enhancing the brain activity, and their consequent refractory effect, are not well understood. In this work, we use a neural field theory (NFT) thalamocortical model to predict and evaluate the changes in the cortex activity to different open-loop and phase-locked sensory stimulation pattern. The selection of model parameters can influence the power of slow-wave sleep (N3 stage) and the occurrence of spindles. Using a linear approximation of the NFT model, it is possible to obtain an analytical output generated as a response to small amplitudes stimulation. However, the linear approximation is not enough to characterize the phenomenon given the nearness of the model operation point to the spindle instability boundary. For this, we generate numerical simulations to obtain the model response dynamics for open and closed-loop stimulation. As a result, we observe that the sensory stimulation enhances the model response at the stimu- lation frequency, but also, for larger amplitudes, it could drift the steady-state response and change its temporal dynamics. The enhancement magnitude at a given frequency depends on the baseline dynamic before the stimulation.

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74) Active behavior is characterized by changes in primary visual cortex dynamics and sensorimotor long-range synchronization

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Classical approaches to understanding sensory systems, studied the brain responses to externally delivered stimuli, either under anesthesia or during strong motor constraints. Nevertheless, during natural behavior, organisms are actively engaged when perceiving their surroundings, in such a way, that action induces changes over sensory organs in a precise manner. We recently showed that under active behavioral paradigm, rats have a better performance on detecting a brief visual stimulus, when compared with their performance under conditions with externally delivered stimulus, as on classical approaches. This is consistent with the evidence in several sensory domains and from a variety of species, showing that active behavior is associated with several functions, such as inhibiting irrelevant sensory stimulus or enhancing sensory processing. We studied the neural correlates of this active behavior on primary visual (V1) and secondary motor (M2) cortices, by recording LFP activity of right or left hemispheres, during active (AC), passive (PC) and motor uncoupled (MUC) conditions. On the AC rats learned to detect a brief left or right light, that was elicited immediately after releasing a central lever on an operant conditioning chamber. On the PC the stimulus was externally delivered, and on the MUC a variation of the AC was tested, where a random time interval was introduced between the motor act of releasing the lever and the stimulus presentation. We found that V1 but not M2 showed a strong modulation of the visual evoked responses during AC compared with PC. This strong modulation was not observed after uncoupling the motor act and sensory stimulation on the MUC. Additionally, left and right stimulus elicited marked lateralized responses on both M2 and V1, on PC and MUC. The lateralized response observed was almost completely abolished during AC. Finally, we studied phase synchronization between M2 and V1 LFPs after stimulus presentation. We found that M2 and V1 are briefly synchronized after stimulus presentation and that the level of synchronization varied across PC, AC, and MUC. Altogether, these results show that active behavior strongly modulates processing of sensory stimulation on V1 and is associated with changes in long-range synchronization between V1 and M2. Importantly these changes depend on the precise coordination between the motor act and the sensory stimulation.

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75) Saccade-Related Potentials (sacRP) during a free visual task on non-human primates

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It is known that when visually exploring a scene freely, primates perform on average four eye movements or saccades per second. This implies that the segmentation of the scene, the acquisition of the characteristics, and the identification of the components of the image must be obtained in a period of 200 ms. In previous studies, it has been shown that in the primary visual cortex (V1) of monkeys in free visual tasks, the synchronization of the peaks related to the fixation occurs in the early phase of the frequency response after the start of the fixation; suggesting a specific role of the peaks of the first response in the V1. On this work we explore the saccade-related potential (sacRP) of local field potential (LFP) recorded with multi-electrodes on V1 of two primates simultaneously to eye-movement recording. The subjects performed a free exploration task where natural images were presented for 5 seconds; we obtained around 20 saccades per image. Our results so far show a positive peak in the signal around 70 ms after saccade onset. This modulation of the LFP signal locked to saccade onset indicates a modulation in neural excitability. And suggests that both the individual spikes and the LFP signal would be part of the same phenomenon.

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76) Chromatic pupillometry for the characterization of the pupillary light reflex in *Octodon degus*

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The common degu (*Octodon degus*) is an emerging model in biomedical science research due to its longevity and propensity to develop human-like conditions. However, there is a lack of standardized techniques for this non-traditional laboratory animal. In an effort to characterize the model, we developed a chromatic pupillometry setup and analysis protocol to characterize the pupillary light reflex (PLR) in our animals. The PLR is a biomarker to detect early signs for central nervous system deterioration. Chromatic pupillometry is a non-invasive and anesthesia-free method that can evaluate different aspects of the PLR, including the response of intrinsically photosensitive retinal ganglion cells (ipRGCs), the disfunction of which has been linked to various disorders. We studied the PLR of 12 degus between 6 and 48 months of age to characterize responses to LEDs of 390, 450, 470, 500, 525 and 605 nm, and used 5 with overall better responses to establish a benchmark for healthy PLR (PLR+) and deteriorated PLR (PLR-). Degu pupils contracted up to 65% of their horizontal resting size before reaching saturation. The highest sensitivity was found at 500 nm, with similar sensitivities at lower tested intensities for 390 nm, coinciding with the medium wavelength and short wavelength cones of the degu. We also tested the post-illumination pupillary response (PIPR), which is driven exclusively by ipRGCs. PIPR was largest in response to 450 nm light, with the pupil preserving 48% of its maximum contraction 9 seconds after the stimulus, in contrast with 24% preserved in response to 525 nm, response driven mainly by cones. PLR- animals showed maximum contraction between 40% and 50% smaller than PLR+, and their PIPR almost disappeared, pointing to a disfunction of the iPRGC pathway rather than the retinal photoreceptors. Our method thus allows us to non-invasively estimate the condition of experimental animals before attempting other procedures.

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77) Influence of the Light Intensity on the Neuronal Spike Distribution of Retinal Ganglion Cells in *Octodon degus*

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The understanding of the mechanisms of neural coding represents an important challenge for neuroscience. We evaluate here the influence of a controlled simplistic parameter, the light intensity, on the firing spike response of Retinal Ganglion Cells (RGC).The physiological responses of a RGCs recorded from isolated retinal patch of young *Octodon degus*, a diurnal rodent, was characterized using a Multi Electrode Arrays (USB-MEA256, Multichannel Systems, Germany) using 256MEA100/30iR-ITO matrices and sampling at 20.000 Hz. Twenty light intensities split in 5 levels (from 20% to 100% of the maximum) and attenuated by four filters ND5 to ND2 (Thorlabs, USA) corresponding to 10-5 to 10-2 multiplying factor were used. A light flash of 400ms was followed by a dark flash of 1000ms. For each intensity, experiments were repeated 30 times. Spike distributions of the first 400ms (ON part) were analyzed using time-frequency approach, with a moving Hanning windows (durations from 20 to 200ms) in order to determine the maxima of the skype frequency and their temporal positions. The RGCs responses can be interpreted as a spike frequency varying in time as an attenuated chirp resonator depending on five parameters: an initial $t0$ and four frequencies, denoted $f0$ to $f3$ as $f(t) = f0 \cos(2\pi f1(t-t0)[1- f2(t-t0)]) \exp(-f3(t-t0))$. The measured frequency values were normally distributed (except for $f0$) with mean and standard deviation equal to $f1 = 17.0\pm3.7$, $f2 = 2.2\pm0.8$ and $f3 = 4.1\pm2.7$ Hz. It was observed that $f1$ and $f2$ were correlated (Pearson's $R2 = 0.48$, $p< 10\text{-}5$) while no correlation was found with $f3$. The initial time values were found equal to 83±33ms. The mean (over the RGC population) values of all parameters varies with intensity except for $f1$. The median value of $t0$ and $f2$ decreased with the intensity with $R2$ equal to 0.66 and 0.49 respectively while $f0$ increased ($R2 = 0.84$). All correlations were associated with p values inferior to 0.001. Finally, it was observed that the maximal values were distributed close to the temporal positions of oscillator which parameters are the mean parameter values of the all responses suggesting the presence of a common oscillator. This study highlighted the presence of underlying oscillators in the responses of *O.degus* RGCs, which parameters varies with the light intensity. This study opens perspective in the exploration of different mechanism for retina neural coding.

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78) Neuro-mimetic lexical-semantic analysis for retinal data

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The retina, with two synaptic layers and many different cell types, has been shown to perform not only as a transducer but as a processing subsystem. Retinal Ganglion cells (RGCs) receive activity mainly from amacrine and bipolar cells, sending its spiking activity to the brain through the optic nerve. The conversion of the visual scene to the RGC spiking activity encodes and compress the visual information following constraints imposed by the channel capacity and energy consumption. Given that higher visual areas receive activity sent by RGCs, then those, in turn, should have the ability to understand a coded message to generate an action. Also, spatial, temporal, and spatial-temporal spike patterns have been proposed to conduct information as units, identified as structured cell assemblies. In this work, we interpret the information encoded by RGCs as language messages. Accordingly, we propose a Neuro-mimetic Language Model (NLM) introducing a neural-word definition, which can be evaluated using Natural Language Processing (NLP) algorithms. In particular, we expect to identify in the retina activity semantic structures, i.e., clusters of words with similar meaning. For this, we apply a corpus-based NLP techniques (i.e., matrix-factorization representation), so as to determine relevant semantic closeness via Latent Semantic Analysis (LSA) and word topics clusters via Latent Dirichlet Allocation (LDA). These techniques are assessed in in-vitro retina recordings from the Octodon degus, under different natural and artificial stimuli conditions. Our central claim is semantic structures only emerge for evoked activity, mainly for movies of the natural animal environment. Moreover, we expect that comparisons between spontaneous and evoked activity shed light over the coding retina strategies for different types of stimuli. Besides, the semantic structures emerged across different individuals are hypothesized to determine inherent cross functions of the retinal design. As a preliminary advance, neural-lexeme has been defined for one-neuron-one-word mappings setting a limit to the model lexicon size, i.e., the number of basic abstract units of meaning, to the number of recorded neurons in the experiment. It also mixes spatial and time correlations when analyzing with a global method. A more complex lexeme definition may be introduced to allow lexemes to account for semantic content, from a population coding point of view. Preliminary, better clustering scores have also been observed for natural movies recordings.

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79) Inhibitory activity in the OFF retinal pathway is altered in a lens-induced myopia mouse model

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Myopia or nearsightedness is the most common cause of impaired vision worldwide, and has reached epidemic levels in several Asian countries, notably China, South Korea and Japan. It is generated by progressive axial elongation of the eye, which results in an insufficient focal length for the viewing of distant objects. The retina is known to play a critical role in the regulation of ocular elongation, as it detects changes in focus and sends signals to the pigment epithelium, where growth factors are thought to be released towards the sclera to regulate the growth of the eyeball. While the precise retinal mechanisms involved in the progression of myopia remain unclear, a decrease in dopamine levels concomitant with an increase in the expression of GABA receptors and transportershas been described in both humans and animal models of myopia. Moreover, it is known that dopamine, which is released depending on overall illumination levels, differentially modulates the inhibitory signals in the visual ON and OFF pathways. However, it is currently unknown whether changes in dopamine levels can be related to a differential modulation of inhibitory activity in retinal ON and OFF pathways during the progression of myopia. To verify whether inhibitory activity in the inner retina is affected under myopic conditions, a concave monocular lens (of -10 diopters) was placed on one mouse eye for a period of ten days in order to generate a lens-induced myopia model. Under light-adapted conditions, a significant increase in the frequency but not the amplitude of inhibitory activity was observed in OFF bipolar cells, whereas a reduction in the frequency of inhibitory activity was found in OFF ganglion cells in treated eyes compared to control. In contrast, under scotopic conditions, an increase in both the frequency and amplitude of inhibitory activity was observed in OFF bipolar cells, while no significant changes were found in OFF ganglion cells. Remarkably, in the ON pathway, inhibitory activity in both bipolar and ganglion cells was unaffected under both light and dark adaptation. Altogether, our findings suggest that after ten days of myopia induction, inhibitory activity is altered in the OFF pathway, but not in the ON pathway. These observations could reflect an important mechanism involved in the progression of myopia. Further experiments are necessary to determine how exactly inhibitory signaling in the OFF pathway is modulated during different stages of myopia progression, and how this modulation is related to pathologically altered eye growth.

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80) Cholinergic Modulation of Stimulus-Specific Adaptation in Primary and Secondary Rat Auditory Cortex

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In the auditory cortex, there are neurons that specifically decrease their response to repetitive sounds (standard tones) but that increase their firing rate against novel stimuli (deviant tones); the difference between both responses is known as stimulus-specific adaptation or SSA. This study describes the cholinergic modulation of SSA in rat auditory cortical areas. Here, we measured SSA levels in single neurons of primary and secondary auditory cortical areas, in response to oddball auditory paradigms, before, during and after the microiontophoretic application of acetylcholine (Ach). As a control, in a subset of neurons we also applied cholinergic antagonists of muscarinic (scopolamine) and nicotinic (mecamylamine) receptors. We observed that SSA (measured as the common SSA index, or CSI) was increased for most of the recorded neurons (65/80) after the application of Ach. These changes were produced by a selective increment in the neuronal firing rate in response to the deviant tones (0.82 ± 0.18 spikes/s control vs 1.61 ± 0.23 spikes/s Ach, $p < 0.001$). By contrast, the response to the standard tones was not affected (0.40 ± 0.13 spikes/s control vs 0.41 ± 0.15 spikes/s Ach, $p = 0.546$). Furthermore, we found that the effect of Ach on SSA was mediated by muscarinic receptors, since the application of scopolamine decreased SSA (CSI = 0.62 control vs CSI = 0.55 scopolamine, $p < 0.001$) and SSA was unaffected when blocking nicotinic receptors (CSI = 0.58 control vs CSI = 0.55 mecamylamine, $p = 0.392$). We conclude that cholinergic modulation in the auditory cortex increases SSA by selectively increasing the neuronal firing rate in response to the deviant tones and this modulation is mediated mainly by muscarinic receptors.

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81) Target detection Task in an Oddball Context: A New Training Protocol for Rats

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How the brain deals with the conflict between what is likely to happen and what is behaviorally relevant remains unknown. In previous works, we have used the oddball paradigm to study stimulus-specific adaptation (SSA) to assess neuronal responses to standard (regular and repetitive) and novel, deviant stimuli in the auditory brain. Thus, in order to evaluate SSA (what is likely to happen) modulation during an attentional task, we have trained rats to discriminate deviant tones as in an oddball paradigm.For this, we have designed three levels of complexity with food rewards where the animals learn first to respond to a sound activating a nose-poke in an operational chamber. First, animals learnt to respond to a sound activating a nose-poke in an operational chamber, then they learnt to recognize a deviant tone presented in between periods of silence, and finally they learnt to distinguish a deviant tone embedded in an oddball paradigm. At the end of the training, data were collected after three oddball paradigms options: 1) the classical paradigm, high probability standard tones (90%) randomly interrupted by low probability deviant tones (10%) and 0.5 octaves in frequency contrast, 2) a similar paradigm, but in this case, the frequency contrast between standard/deviant tones varied in 3, 0.25 octaves steps, and 3) a many deviants sequence made of several blocks of the classical oddball paradigm as 1, where every 10 stimuli, the sound frequency of the a deviant tone is randomly changed from 9 possibilities of different tones, and the standard sound is maintained throughout the entire sequence. To quantify the ability discrimination of the rat, we calculated the conventional *d'* index and we implemented options 2 and 3 to test the animals' responses to irregularity. Results so far (n=19) show that trained animals were able to complete this target-detection tasks with 70.1±14.6% of correct detections, 8.6±4.8% of false alarms, and a *d'* value of 2.1±0.6 (mean ± std). Thus, our data demonstrate that rats can successfully discriminate the salience of deviant stimuli. This behavioral study will be useful in future neurophysiological studies in the behaving animal, as it will be the key resource to understand the neuronal link between expectation and attention

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82) Are ocular movements involved in perceptual change in bistable stimuli?

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Bistable perception is a visual perceptual phenomenon where the visual input of the stimulus remains invariant, but our perception of it changes. It has been described that eye movements could increase the probability of experiencing a perceptual change. So far, the particular event linked to the act of transiting between two perceptual states is still unknown. In the present work, we evaluate the specific role of ocular movements when a visual perceptual switch is reported. We recorded perceptual switch reports, electroencefalographic activity and ocular behavior from 27 subjects who had to observe 3 bistable stimuli in 4 conditions: free exploration, restriction of eye movement, rapid change and hold perception. Our results show that subjects consistently and repetitively explore certain regions of the bistable stimuli, independent of dynamism or condition. Although the occurrence of saccades shows an oscillatory behavior around the time of reported electroencephalographic changes (700 – 400 ms before the reversal report), this oscillatory behavior has different frequencies across subjects. Other saccade characteristics, as amplitude or direction of eye movement, are not directly linked to the perceptual change, because are temporarily ambiguous and inconsistent to the reversal. These results suggest that ocular movements contribute poorly in neural mechanisms related to perceptual switch.

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83) Effect of auditory interference on bistable visual perception in humans

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Our environment presents multiple stimuli simultaneosly, our brain integrates these stimuli to achieve a coherent perception thus shaping our behavior. Understanding how the characteristics of stimuli influence sensory integration is important to comprehend this phenomenon. Evidence shows that the stimulus in one sensory modality influences the perception of another stimulus in a different modality, especially when the latter is ambiguous and therefore difficult to perceive. However, so far we don't know which stimulus characteristic on one modality disambiguates the perception on other modality to generate a perception coherent with the environment. Here, we investigate how the direction of a stimulus in one sensory modality influences the perception of direction on other modality. Particularly, we studied in humans whether the direction of a sound biases the perceived direction of a visual bistable stimulus. Subjects were in a totally dark room and sit in front of the screen where we presented a "structure from motion" visual bistable stimulus. This bistable stimulus can be perceived either rotating to the right or to the left, and subjects' task was to report each time they experienced a change in the movement direction. Simultaneously we delivered an auditory stimulus that had direction left-to-right or right-to-left. Thus, on any trial the auditory stimuli might reinforce the current visual perception when both modalities were coherent, or destabilize the visual perception when they were not. We evaluated the effect of sound direction on visual perception in 14 volunteers. We found longer periods of perceptual stability when visual and auditory stimuli where coherent compared to incoherent conditions. Changes in the level of attention evoked by the auditory stimuli cannot explain the results.This finding suggests that the characteristics of the disambiguating stimulus participate in the process of multisensory integration, and that these would be necessary for this phenomenon, but not sufficient, since sensory integration would be a process that uses various resources simultaneously to form a perception that is stable and consistent with the environment.

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84) Design of a saccade-contingent paradigm for active visual exploration

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Under the Predictive Coding framework, the visual system is understood as a hierarchical system that constantly makes predictions about the visual surroundings. During active visual perception, each eye movement or saccade is associated with a prediction of the sensory information expected at saccade landing position. Saccades are ballistic movements, once initiated new information cannot modify its trajectory; thus, allowing to introduce contingent changes on the visual scene without interfering eye movement trajectories. In such a context, we could test the predictive coding hypothesis relative to saccades by changing the image content at the saccade-landing site. But, so far, we lack paradigms to introduce changes contingent to saccadic movement during free visual exploration. In the present work, we adapted and tested a model from virtual reality to predict saccade-landing position during exploration of natural scenes; and made contingent manipulations on these same locations. On this model, the current saccade‘ onset is detected and its landing position predicted based on its previous positions. This allowed the manipulation of the image contingent to saccadic movement, which occurred at different intervals around the end of saccades, and at different distances from the gaze central position. Specifically, subjects observed several natural scenes while their eye movements were recorded. The manipulation consisted on the introduction of Gabor patches, and subjects were asked to report their perception of the patch, particularly its location and moment of appearance. When we tested the model we found that 90% of the predicted positions were within 5 visual degrees of the actual position of saccade landing and that 90% of the predicted patches were drawn between 50 ms before and 20 ms after the end of the saccade. When we analyzed the subjects report we observed a positive linear relation between the physical distance from patch-center to gaze-center and the perceived distance reported by subjects. We also studied the timing of the change, and we found that for patches appearing within 2.5 visual degrees from gaze-central position, there was a significant but small relationship between the perceived time of patch drawing and the actual manipulation time. This relation was absent for larger distances. Altogether, these results suggest that the saccade-contingent paradigm introduces changes that are both precise in time and space during active exploration of natural scenes. Also, the relations between the subject report and patch location suggest that subjects are more aware of changes occurring within a close distance from the gaze center.

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85) Eye movement awareness without saccadic eye movement: Could be eye movement awareness related to a shift on attention instead of eye movement itself?

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Every day we are faced with numerous stimulus in our surroundings and many times we shift our attention to peripheral locations without making a saccadic eye movement. This extrafoveal attention while gaze is maintained on a fixation stimulus is called “covert attention”. During eye fixation, tiny and quick eye movements take place which is called microsaccades. Recent studies had suggested that covert attention can be directed towards the stimulus through microsaccades execution. In previous covert attention experiments, we could notice that after task realization a few subjects reported the sensation of having made saccadic eye movements in some trials. However, experimental data analysis did not show any saccadic eye-movement. Thus, the following question arises: Could eye movement awareness be related to this shift on attention during covert attention task instead to be related to saccadic eye movement itself? To explore this question we designed a covert attention task focused on self-report of eye movement perception. In brief, each trial consisted of an emotional face presented 28º to the left of a fixation cross for five seconds. Participants were required to identify the facial emotion by verbal report while they were strongly encouraged to maintain their gaze into the fixation cross by telling them this fixation was essential for the task. Subjects were instructed to report as soon as possible if they perceived having done any eye movement during fixation time by pressing a joystick button. The participants were naive to the purpose behind the task. Eye movements were recorded using eye-tracker, face images were obtained from KDEF database and the task was designed with 4 blocks with 10 trials each. Eye positions and speed of eye movements were analyzed up to 1000 ms before the self-report. About 80% of the subjects reported having moved their eyes (from 1 to 31 times during the task). Of the perceived eye movement reports, only about 25% were saccadic eye movement greater than fixation cross length (2º), while the other 75% reports corresponded either to microsaccades (amplitude less than 1º) (~45%) or to movements inside the fixation cross (~30%). In terms of eye movements speed, about 70% showed speeds >0.1°/s. Our findings suggest that eye movement perception during fixation is not related to the saccadic movement itself. It remains to be determined how this perception could be related to a shift on attention or to microsaccade execution
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86) Improvement of performance in facial emotion recognition using peripheral vision in low vision subjects with central vision loss

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While visually exploring the environment, people centralize objects of interest to the fovea. But when the fovea is damaged, as in many Low-Vision (LV) patients, central vision is lost and no longer useful for seeing. Patients start using systematically one or more peripheral retinal regions called preferred retinal loci (PRL) to perform visual tasks, centralizing objects to this PRL. This is also accompanied by neuroplastic events as changing the retinotopic map in V1 or re-referencing eye movements to this region instead of the fovea. Moreover, their performance using their PRL in some visual tasks that require high visual acuity, like reading, can be improved by training. But, ¿can we exploit these neuroplastic events and train people in using their peripheral vision to improve their performance in more complex visual tasks, such as facial emotion recognition? We explore this question by training peripheral vision of 4 low vision (LV) subjects with central vision loss for 5 sessions (5 weeks; 1 session/week) in a facial emotion recognition task, while their eye movements were recorded using an eye tracker. The task consisted of 4 blocks of 10 trials each. In each trial, a face with or without emotion was presented. Subjects were instructed to explore the face and press a button as soon as they recognized whether there was an emotion or not (emotion recognition) and, if there was, which emotion was displayed (emotion identification). After pressing the button, they answered aloud which emotion (if there was any) they identified. The percentage of emotional faces correctly recognized and identified and the time required for identification were registered and compared between training sessions. LV subjects who had an initial performance comparable to normally sighted subjects (about 85% in emotion recognition and about 75% in emotion identification) do not significantly improve with training. On the other hand, the subject with the worst initial performance (67.5% in emotion recognition and 60% in emotion identification) significantly improved her performance through training, reaching a 97.5% in emotion recognition and 90% in emotion identification. Also, this improvement was preserved after 10 weeks without any further training. These results support the idea that peripheral vision can be trained to perform a complex visual task such as facial emotion recognition in LV patients with central vision loss. However, it also shows that not all patients would benefit from this training, but only those whose initial performance is diminished.

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87) Otoacoustic emission amplitude and the olivocochlear reflex strength are associated with anxiety and quality of life in tinnitus

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Tinnitus is a symptom characterized by the perception of sounds that is not originated from an external sound source. According to epidemiological studies, there is a high prevalence of tinnitus in the world population (e.g. 8 to 25.3% of the population of the United States), and it is associated with psychological problems like anxiety, distress and depression. The auditory efferent system is a neural network that comprises descending projections from the auditory cortex to the cochlear receptor, reaching the outer hair cells through the medial olivocochlear (MOC) fibers. Despite a large number of studies in tinnitus and auditory efferent system, it remains unclear whether there is a relationship between medial olivocochlear function and tinnitus. In addition, to our knowledge, there is a lack of literature that associates MOC function with anxiety and quality of daily living in tinnitus. The functionality of the inner ear, specifically of the outer hair cells, can be assessed by distortion product otoacoustic emissions (DPOAEs), while the MOC function can be assessed by measuring the olivocochlear reflex (OCR) strength through DPOAEs amplitude changes induced by contralateral acoustic stimulation (CAS). Here, we recruited 26 tinnitus patients between 22 and 60 years, mean age= 41.8 years, with normal audiogram thresholds (average PTA in the right ear=10.1 dB and in the left ear=8.5 dB). Subjects were evaluated with a complete audiological battery and psychometric questionnaires. We found that larger DPOAEs amplitudes of the left ear are related with more disabling tinnitus as evidenced by the Tinnitus Handicap Inventory (THI), and that reduced OCR strength of the left ear is related with more anxiety as evidenced by the State-Trait Anxiety Inventory (STAI). Our preliminary results suggest a relationship between inner ear function and OCR strength with *self-perceived quality of life and anxiety* measurements in tinnitus sufferers.

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88) A window to the brain: changes in pupil diameter during visual fixation relate to EEG alpha activity fluctuations

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The mammalian thalamocortical system generates intrinsic activity that manifests in different states of excitability related to membrane potential changes of the underlying neural networks. Neural networks undergo constant, spontaneous, state fluctuations triggered by changes in this internally generated activity that influence stimulus encoding, information processing, and neuronal and behavioral responses. These variable activity patterns vary on long and short time scales and shape the continuous signal, as well as the neuronal responses to incoming sensory information. At the behavioral level, these states can be linked to different levels of arousal and attention and other non-sensory signals directly related to behavioral performance; highlighting the need for a systematic study of state fluctuations aimed to investigate their influence on ongoing neural recordings. Recent studies in head-fixed rodents have shown a direct relationship between changes in pupil diameter and network states, possibly because both are controlled by the release of acetylcholine and norepinephrine. Therefore, we hypothesize that monitoring pupil dynamics would also allow to infer different states in the human brain by means of a non-invasive measure. We studied the EEG signal associated with pupil dynamics of 10 healthy volunteers while they were fixating the center of a gray screen for one minute. The pupillometry recordings show spontaneous fluctuations in pupil diameter during fixation period, evidencing intervals of peaks and troughs. Focusing EEG analysis on time windows surrounding those two events, we found an increment in alpha band amplitude in parietal-occipital channels during peaks compared to troughs. Additionally, alpha activity was differentially modulated for on- and offsets of peaks and troughs. An increase in alpha amplitude was observed before peak onset and a reduction in alpha amplitude was observed after the peak. Conversely, for troughs, alpha amplitude showed a reduction before their onset and an increase after. Together, these results suggest that spontaneous variations of pupil diameter can indicate changes in cortical activity that may reflect fluctuations in the ongoing state of the cortical network, and the underlying neuronal excitability. These results further our understanding of task-independent variations in neural and behavioral signals, previously overlooked as noise. ICM P09-015-F; CONICYT, FONDECYT/Postdoctorado 3140306 to CD.

89) Pupillometry and EEG source modeling reveal different brain dynamics during conscious and subconscious processing of acoustic irregularities

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The brain's ability to detect violations of auditory predictions is at the core of sensory and executive processes, modulating both automatic and goal-oriented behavior. Brain response to acoustic anomalies classically involves a frontocentral negativity (MMN) between 150 - 200 ms post-stimulus onset, independent of attentional state and conscious control and a central positivity at around 300ms (P3) post-stimulus onset which depends on attention and conscious control and associated with goal-directed behavior. While MMN generators in the Superior Temporal Gyrus and frontal regions have been proposed, different generators over a fronto-cingulo-parietal network have been suggested for the P3 event. These different sources possibly reflect the involvement of distributed attentional networks over the time course of auditory novelty processing. Here, we tested whether conscious and subconscious processing of auditory anomalies translates into distinct neural dynamics with task-relevant effects. For this, we first implemented an auditory staircase procedure to identify the discriminatory threshold (the minimum frequency contrast between two tones so that participants can identify them as different tones) of each subject. Using this procedure, we defined a standard stimulus (the lower-end tone of our staircase), a below-threshold stimulus (the tone that was two steps below each subject's discriminatory threshold), and an above-threshold stimulus (the upper-end tone of the staircase procedure). With these stimuli, we designed a modified version of the auditory oddball task. We presented variable trains of standard tones where the last stimuli could be another standard, a below-threshold tone, or a beyond-threshold tone. After each train of tones, we asked participants to decide by pressing one of two buttons whether the last tone was different or the same as the previous ones. Preliminary results (10 subjects) reveal that although subjects judge below-threshold tones to be the same as standards and correctly identify above-threshold to be different, behavioral, electrophysiological and pupillometric differences underlie the processing of the three different target stimuli (target standard, below-threshold, and above-threshold contrasts). Source modeling also reveals a possible lateralization effect that differentiates subconscious from conscious processing of acoustic irregularities. These results suggest that although subjects report is binary (same or different), both behavioral, psychophysical and electrophysiological dynamics disambiguate conscious and subconscious processing of standard and odd tones.

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90) Catecholaminergic treatment does not modulate the late posterior potential and alpha-band power of ADHD children during a visuospatial working memory task

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Deficits in visuospatial working memory (VSWM) are a common impairment in children with ADHD. Electroencephalography studies have found modulations in ADHD children of amplitude and power at different latencies and frequencies of event-related potentials and oscillations, during memory tasks. For instance, the late posterior potential (LPP) is thought to reflect recognition and alpha oscillations are relevant for working memory maintenance and coordination of brain areas. Moreover, ADHD has been proposed as a catecholaminergic signaling disorder. However, no study has evaluated the role of ADHD catecholaminergic treatment on brain activity during a VSWM task. In this study, we compared the modulations of late ERP components and low-frequency oscillations between typically developing (TD) and ADHD children (9-13 yo) in a modified Sternberg VSWM task. Furthermore, to study the role of catecholaminergic treatment in VSWM, ADHD children performed the task in two separate sessions, on- and off-medication, which in all cases was methylphenidate. The reaction time (RT) and standard deviation of RT did not vary between groups. However, accuracy was lower in ADHD children than in TD children. The ERP analysis revealed significant decreases of the LPP starting at 300 ms between TD and ADHD children, independently of medication, during the encoding and recognition phase of the task. MPH On and MPH Off children presented no differences. The spectral analysis revealed differences between TD and MPH Off children in the central alpha-band around the RT period (300-600 ms). Moreover, the latency of the peak of alpha desynchronization during the RT period (300-600 ms) was reduced in ADHD children. To further study the relationship between alpha and behavior, we performed correlations maps between the time-frequency data and subjects RTs. We found that the power in the alpha band was positively correlated with RT during the encoding period and negatively during the recognition period only in control children. These results suggest that ADHD children deficits in VSWM might be due to changes in neural activity, Additionally, catecholaminergic medication apparently does not improve performance in a VSWM task.

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91) Impact of cerebellar tDCS stimulation on working memory oscillations of spinocerebellar ataxia patients – a pilot study

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Spinocerebellar ataxias (SCA) are rare neurodegenerative disorders that are a heterogeneous group of pathologies associated with cerebellar degeneration and its afferent and efferent pathways. This leads to the appearance of various motor symptoms that include imbalance, gait disturbances, dysarthria, tremor of intention, incoordination of the limbs and also to alterations of executive functions. At present, degenerative ataxias lack adequate symptomatic treatments. Transcranial direct current stimulation of the cerebellum (ctDCS) is a non-invasive brain stimulation method that has shown positive preliminary results on some motor symptoms in patients with SCA in both the short and long term. Considering the great need for new therapeutic strategies, this study seeks to explore the impact of ctDCS on motor and cognitive symptoms, in particular working memory, that characterize and affect the quality of life of these patients. Ten patients with SCA were recruited and randomly assigned to treatment (patients receiving ctDCS) and a control group (patients receiving sham stimulation). A 2mA anodal ctDCS or sham stimulation protocol was applied over a period of two weeks. Behavioral and electrophysiological measures of working memory were evaluated before and after stimulation with a variant of the Sternberg Memory Task and electroencephalographic recordings (Geodesic 64-channel EEG). Behavioral and EEG data are being analyzed and preliminary results will be presented at the conference. We expect to find an improvement in working memory performance and modulations in midline frontal theta oscillations (~4–8 Hz) associated with focused attention and beta oscillations (~13–30 Hz) associated with endogenous (re)activation of cortical representations in the group of treated as compared to control patients.

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92) Effects of visual working memory load on the olivocochlear reflex strength and early auditory evoked potentials

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Top-down influence of selective attention on irrelevant sensory stimuli has been proposed as a mechanism that help to maintain relevant information in working memory. In visual working memory (WM) tasks, modulation of distracting sounds has been seen in cortical and subcortical stages of the auditory pathway. Weather this influence of selective attention is presented at the level of the cochlea has not been assessed yet. Here we ask whether distortion product otoacoustic emissions (DPOAEs), sounds produced as sub product of the cochlear amplifier, and cortical auditory evoked potentials N1-P2 are modulated by visual WM load. Twenty subjects (twelve male, age range 20-31, mean age 25.2 years) with normal hearing performed a visual change detection task with varying working memory load (high load= 4 objects; low load = 2 objects). The olivocochlear strenght was measured using the DPOAEs, by the effect of adding contralateral acoustic stimulation (CAS) in half of the trials. Auditory stimuli (frequency range 1250-2200 Hz) with and withouth CAS were delivered simultaneously with the task to measure DPOAEs and N1-P2. Results showed a modulation of DPOAE magnitude only in the high visual WM load with CAS condition. Additionally, DPOAE suppression by CAS was increased by visual WM load. N1-P2 magnitude was modulated by working memory load but no relation was found with DPOAEs changes. Finally, working memory task performance was correlated negatively with P2 amplitude, a result in agreement with the view of selective attention as a mechanism to protect limited WM limited resources from irrelevant sensory stimuli. The results of this study showed that peripheral and cortical processing of auditory stimulus can be modulated by visual WM load, and that cortical processing of distracting stimulus can be a predictor of visual WM performance. This study helped to clarify the interaction between selective attention and WM in the processing of distracting stimulus.

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93) Neurophysiological and behavioral correlates of auditory contextual emotional processing in healthy adult women: Description of the loudness dependence auditory evoked potential

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Major depression disorder (MDD) is one of the most prevalent psychiatric disorders in Chile affecting more women than men. MDD is described as a set of affective and cognitive symptoms associated with a dysfunction of the serotonergic system. Several studies have correlated serotonergic activity with the modulation of an event-related potential (ERP) component called Loudness Dependence of the Auditory Evoked Potential (LDAEP), which is evoked by tonal auditory stimuli without emotional valence, and whose amplitude correlates with serotonergic activity, psychophysical performance and emotional sensitivity. Here we evaluate whether the LDEAP is elicited by a novel version of the auditory oddball paradigm using stimuli with emotional valence and if it is correlated with psychophysical indicators and the emotional sensitivity scale of the Inventory of Beck (BDI) in healthy female population. We sought to describe and explore changes in LDAEP component as well as in psychophysical indicators, mainly reaction time and false alarm, in a task of detection and recognition of emotional auditory stimuli (positive, negative, neutral). Behavioral and electroencephalographic (EEG) data from 10 female subjects was obtained using a modified auditory Oddball paradigm. There were 3 conditions: (1) standards were negative and distractions were positive (PD), (2) standards were neutral and distractions were positive or negative (OD), (3) standards were positive and distractions were negative (ND). In addition, the BDI was conducted to assess the emotional sensitivity of the participants. Behavioral analysis indicates that the percentage of false alarms presented a statistical difference ($p < 0.001$) between PD and OD condition. In reaction times (RT) and total accuracy, percentage of correct responses between standards and distractors have a significant difference within their same category, but not between the categories (ND, OD, PD). This suggested that emotional processing depends on the physical properties of the stimuli, affecting behavioral performance. For EEG analysis, we describe for the first time that the LDAEP is elicited with auditory stimuli with emotional valence. Scalp analyses show an increase in power (μV) in temporal lobe region at 100 ms and in prefrontal region at 200 ms, which would indicate low level and executive processing, respectively. Finally, Sperman correlation between the LDAEP component and BDI scale values show a trend with a $r \geq 0.8$. This suggests that the LDAEP component evoked by auditory stimuli with emotional valence is a useful tool for assessing emotional regulation and a possible neuro-marker for MDD.

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94) Attentional Modulation of 1/f Intracranial Electrophysiological Noise

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Spontaneous fluctuations occur at different spatial and temporal scale in the brain. Depending on its scale, these activities can show characteristic hallmarks. For example, from a macro perspective, spontaneous brain activity shows temporally synchronous and correlated fluctuations across areas which have been modeled as functionally correlated networks (Bullmore and Sporns, 2009). However, from a more micro perspective, in spontaneous conditions cortical neurons fire action potentials in a seemingly stochastic manner, which extrapolated to an entire population shows a dynamical state that has been coined as an asynchronous irregular state (Brunel et al., 2000). The neurobiological principles that dynamically shape micro-scale spontaneous activity are accessible experimentally. Interestingly, when there is a local population of balanced excitation and inhibition recurrently connected, the asynchronous population generates a baseline of stochastic perturbation over the neuron's membrane potential of that local population (Destexhe et al., 2003). These perturbations have been proposed as optimal for information computation (Zerlaut and Destexhe, 2017). At the behavioral level, asynchronous state has been associated with different levels of attention and arousal (Reimer et al., 2014). Specifically, catecholaminergic modulation that regulates brain states are highly implicated in neuropsychiatric disorders and affect cognition, behavior, and perception and it has been implicated in the modulation of asynchronous activity (Pfeffer et al., 2018). An appealing alternative to link behavior with macro and microscale activity is electrophysiology, like intracranial electroencephalography. Interestingly, the asynchronous population activity has been related to signal features, such as its desynchronization. More specifically, recent work has suggested that shifts in the canonical 1/f power spectral density (PSD) relates to background stochastic activity and E-I balance (Gao et al., 2017; Voytek et al., 2015). Here we will show preliminary results that show that background stochastic activity can be separated from oscillatory activity and that this activity fluctuates according to the attentional demand, and tracks canonical macroscale networks related to attention.

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95) Infrasonic oscillations in brain and cochlear simultaneous recordings during selective attention tasks in tinnitus

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Tinnitus is the perception of a phantom sound without any external physical sound source. This symptom usually arises after deafferentation of the cochlear receptor as a consequence of an acoustic trauma. The neural correlates of chronic tinnitus involve several central auditory structures, but also non-auditory brain areas, like the insula and prefrontal cortices, affecting cognitive and emotional functions. The auditory efferent system is a neural network that comprises descending projections from the auditory cortex to the cochlear receptor, reaching the outer hair cells through the medial olivocochlear fibers. The dysfunction of the auditory efferent pathways may also contribute to the generation or perpetuation of tinnitus. In this line, several studies have used contralateral acoustic stimulation to address a possible role of the medial olivocochlear brainstem reflex in tinnitus patients with contradictory results. It also remains unclear whether there is a relationship between tinnitus perception and the functioning of the corticofugal projections from the auditory cortex to the cochlear receptor. Recently, we showed that low-frequency (<10 Hz) cortical and cochlear oscillations are modulated in amplitude and in their temporal properties during a selective attention task to visual and auditory stimuli (Dragicevic et al., PloS One, 2019). Here, we used a similar auditory and visual attention paradigm, and simultaneously recorded electroencephalogram (EEG) and distortion product otoacoustic emissions (DPOAE) in controls and tinnitus patients. We recruited 14 tinnitus patients with normal audiograms (mean age= 39.2 years) and 14 control subjects (mean age= 34.2 years). The amplitude of auditory event related potentials recorded at Cz and Fz EEG electrodes were larger in tinnitus patients (t-test, p=0.002 for Fz and p=0.017 for Cz). In addition, we found a reduction in the amplitude of DPOAE during selective visual attention in controls and tinnitus patients (-0.5 dB and -1.45 dB respectively). Regarding the frequency domain, we found that low-frequency oscillations (<10 Hz) in cochlear (DPOAE) and cortical (EEG) channels were larger during auditory attention as compared to visual attention trials in control subjects (t-test, p=0.002), but not in tinnitus patients. These results suggest that corticofugal mechanisms of selective attention to visual and auditory stimuli from auditory cortex to the cochlear receptor are altered in tinnitus patients.

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97) Two frequency bands to coordinate them all: brain-to-brain synchronization during social interactions

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Brain-to-Brain coupling emerges during social interactions. However, it is not clear whether the inter-brain coupling is an event triggered by simple motor coordination or is a biomarker of complex cooperative behaviors. Here we show that coordination of actions and collaborative dynamics are distinguishing according to the frequency of oscillation in which the brains enter into synchronization. We simultaneously recorded EEG activity in pairs of subjects engaged in cooperative, competitive, and individualistic tasks. In all three versions of the task, sensory stimuli and presentation sequence are the same, varying only the intention with which the participants perform the task in each modality. We found an increase of inter-brain theta coupling (3-7 Hz) during cooperative and competitive interactions, along with a correlation between inter-brain theta values and reaction times. On the other hand, we found an increase of inter-brain gamma synchrony (38-42 Hz) only during cooperative interactions. Inter-brain gamma synchronization was not associated with reaction times. Our findings point to the existence of at least, two different oscillatory mechanisms related to social interactions: (i) a basic low-frequency inter-brain coupling system, triggered by simultaneous performance of the same motor activity, and (ii) a complex high-frequency inter-brain coupling system, induced by co-work guided by common prosocial goals.

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98) Social preferences and cognitive control along human development stages

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The understanding of the complex relationship between cognitive processes and social decision making has been broadly studied in the last decades. This problem has been tackled by different disciplines that have contributed valuable data allowing us to get closer to every particular detail of the multiple processes involved. The objective of this research is to approach the relationship between cognitive control and social preferences along different moments of human development, from behavioral and functional neuroimaging analysis. To achieve this, the behavioral performance and neurophysiological activity of 60 subjects in three different stages of human development (20 children, 20 teens and 20 adults) was measured through a cognitive control task (Go/No-Go) and a social preference task (Trust Game). During this measures, an EEG and fMRI was carried out separately for all subjects. Behavioral results regarding social preferences were found to be correlated to better inhibitory control in the Go/No-Go task and with theta activity related to behavioral inhibition. No relevant intragroup differences were found in regards to social preferences and inhibitory control but, as expected, as age progressed people were found to show higher degrees of behavioral inhibitory control correlating with their different intergroup performances on the Trust Game.

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99) Fronto-parieto-occipital theta activity associated with motor execution in cognitive planning

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The ability to execute a previously elaborated plan is a key function of human cognitive planning. Cognitive planning consists of a sequenced development of a plan to achieve a specific goal (Hayes-Roth et al., 1979), and can be divided into 1) a mental planning phase which consists of internal representation of a sequence of steps (or plans) (Wilensky, 1983), and 2) a planning execution phase which is the motor action to achieve a previously planned goal (Grafman et al., 1991). Behavioral paradigms of planning are a current challenge in cognitive neuroscience, especially when neural correlates are being assessed. In previous results, we have shown that during the planning phase, a strong increase of frontal midline theta activity originating in prefrontal cortex was induced (Domic et al, in preparation). Furthermore, literature suggests that motor control is associated with theta activity in the left dorsal premotor cortex (Pellegrino et al., 2018). However, the precise oscillatory dynamics between both phases are not clearly understood at present. We recorded EEG activity while subjects were performing a novel behavioral paradigm, based on the Zoo Map Task and the Porteus Maze, that evaluated both phases of cognitive planning function. For the planning phase, a maze that represented a zoo map with several paths and four animals inside was presented. Subjects were asked to plan a path visiting all the animal locations following a set of rules. Afterwards, for the execution phase, the maze appeared again, and subjects had to execute the trace planned in the previous planning period using their gaze with a visual feedback that delineated their gaze movement in real-time using an eye-tracker system. Participants showed greater reaction times and decreased performance accuracy during the execution planning period compared to the control condition, suggesting that the planning component of the motor execution phase is more time-consuming, therefore reflecting higher cognitive demand. Moreover, motor execution of a cognitive plan induced frontoparieto-occipital theta activity which could reflect the sensory-motor integration during motor execution of a cognitively controlled planned goal.

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100) Fronto-parietal Coherence and Modulation of Conscious Visual Perception of Facial Expressions

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According to Global Neuronal Workspace Model (GNW), conscious perception of visual stimuli depends on the coordinated activation of posterior and prefrontal brain regions, when these regions are sufficiently activated. Perceptual processing below this threshold is considered subliminal (non-conscious) in contrast processing above the threshold called supraliminal (conscious). The “backward masking paradigm” has been used to study perceptual thresholds using numeric and emotional stimuli. Studies using functional Magnetic Resonance Imaging (fMRI) and Magnetoencephalography (MEG) have shown evidence for the critical importance of functional connectivity between posterior and prefrontal regions for sustaining conscious processing of emotional stimuli in contrast to non-conscious processing. However, the nature of conscious and non-conscious processing of stimuli with positive (e.g., happy) and negative (e.g., sad) valence on the perceptual threshold have not been well understood. Using Electroencephalography (EEG) in this study, we aimed to evaluate the effect of emotional valence of face stimuli on functional connectivity between prefrontal and posterior brain regions of the brain, and its relationship to perceptual threshold for conscious access. A masking protocol is used, in which a **prime** stimulus (a positive or negative face) is presented during 16ms followed by a **mask** (neutral face) of 250ms of duration. Between prime and mask a delay time is presented in the form of blank screen, which is varied trial to trial in a counterbalanced fashion. After each trial, participants evaluate the valence of the face and the certainty of their answer. A 64 channels is used EEG to collect data for this experiment. Preliminary results suggest an increase in coherence at alpha frequency band for supraliminal trials in comparison with subliminal trials, in support of the previous MEG and fMRI results.

101) EEG Functional Connectivity in High Altitude Hipoxia

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High altitude hipoxia is a consequence of the decreasing of oxygen partial pressure when ascending from lowland to higher ground. There is a concern about the effects of the high altitude on cognition and health. In that line, EEG activity is altered in altitude, but little are the reports related to brain connectivity and dynamics. Here, we pretend to characterize Functional Connectivity (FC) and Functional Connectivity Dynamics (FCD) in a group of fifteen (15) healthy subjects in high altitude hipoxia conditions. EEG recordings were taken in situ at 1000 msnm and 4000 msn (high altitude), for a total time of 10 min. We used the power envelope correlation (previously orthogonalization of the signals) as a measure of connectivity. First, we characterized the static FC and used graphs measures to quantify the levels of integration and segregation of the functional network. After, we compute the FCD through sliding windows analysis. The FCD is related to the FC changes of the underlying network, that is, it quantify the temporal evolution of the connectivity patterns. We also computed the variance and speed of change of the FCD, measures related to the FC patterns variability and speed of fluctuations. The project is ongoing, and we hypothesize a reduction of the global efficacy (a measure of integration), and a slowing down of the dynamics (the speed of the FCD) in the condition of high altitude hipoxia. The reduction of these measures could constitutes a brain marker of cognitive impairment in high altitude.

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102) Neural dynamics of the creative process

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Creativity is much more than an artistic expression, creativity is present in everyday life and always brings new things with it, from small innovations to inventions that have radically altered our world and the way we understand and inhabit it (Sternberg & Lubart, 1996) . Creativity has been studied mainly through the contrast between two types of thought (Romo Santos, 1987): divergent thought as opposed to convergent thought (Fink, Benedek, Grabner, Staudt, & Neubauer, 2007) . The divergent thought is the one that before a certain stimulus makes possible a series of answers that have four common characteristics: originality, flexibility, fluidity, and elaboration, on the other hand, the convergent thought always appeals to a single answer that is usually conventional (Razoumnikova, 2000). To measure divergent thinking, psychometric instruments have been created that measure the performance of the subjects studied in two specific domains; verbal domain, which appeals to solve tasks that involve written and/or spoken words and figurative domains that implicate drawing (Plucker & Runco, 1998) . Evidence suggests that the mechanisms involved in each domain would be different (Gonen-Yaacovi et al., 2013; Jung et al., 2010). Most of the electrophysiological knowledge about creative ideation/diverse thought is based on verbal creative ideation tasks, such as the alternative uses task of Guilford (Pidgeon et al., 2016). However, if the reported electrophysiological activation patterns represent general mental processes relevant to the creative ideation such as downward control and internal attention, the study of the creative ideation in the figurative domains should be associated with brain activation patterns different from those observed during the creative ideation in the verbal domain (Wang, Hao, Ku, Grabner, & Fink, 2017). Was designed an experimental paradigm uses a drawing processing task (figurative domain) and, during its development, contrasts divergent thinking with convergent thinking. A experiment was carried out with 22 volunteer participants. We recorded the EEG during a drawing task in which they were asked to draw a symbol associated with a concept as a convergent thinking task versus drawing a new representation for the same concept as another convergent thinking task. The analysis window was the moment of the elaboration of the answer, before the drawing. We find differences in the occipital alpha potency between tasks, with a greater alpha decrease during the divergent thinking task, associated with greater cortical activation, and greater semantic and attentional processing during visual creativity against the baseline. Beca doctorado nacional

103) Enhanced response inhibition and reduced midfrontal theta activity in experienced Vipassana meditators

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Response inhibition - the ability to suppress inappropriate thoughts and actions - is a fundamental aspect of cognitive control. Recent research suggests that mental training by meditation may improve cognitive control. Yet, it is still unclear if and how, at the neural level, long-term meditation practice may affect (emotional) response inhibition. The present study aimed to address this outstanding question, and used an emotional Go/Nogo task and electroencephalography (EEG) to examine possible differences in behavioral and electrophysiological indices of response inhibition between Vipassana meditators and an experience-matched active control group (athletes). Behaviorally, meditators made significantly less errors than controls on the emotional Go/Nogo task, independent of the emotional context, while being equally fast. This improvement in response inhibition at the behavioral level was accompanied by a decrease in midfrontal theta activity in Nogo vs. Go trials in the meditators compared to controls. Yet, no changes in ERP indices of response inhibition, as indexed by the amplitude of the N2 and P3 components, were observed. Finally, the meditators subjectively evaluated the emotional pictures lower in valence and arousal. Collectively, these results suggest that meditation may improve response inhibition and control over emotional reactivity.

103a) The brain-gut-microbiota axis to understand human wellbeing: A promising challenge

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(Sponsored by We Would Like To Thanks Francisco Chavez And Ana Maria Madrid For Insightful Comments During The Production Of The Present Work.)

The brain-gut-microbiota pathway has emerged as an important axis to understand behavior. It has been hypothesized that microbiota communicates with the nervous system by means of bidirectional neural pathways. This communication has been related to the optimal subject's psychological functioning and his or her wellbeing. However, the specific mechanisms underlying such communication are not fully understood. Recently, slow-frequency gastric oscillations coupled with cortical alpha rhythms have been detected. Interestingly, this coupling happens through ascending pathways from the gut, comprising a canonical gastric-brain network. These studies are consistent with the idea that not only brain activity, but also important aspects of psychological life, are not only dependent on intra-brain networks, but also on bodily influences from the gut. We hypothesized that wellbeing is affected by signals coming from the gastrointestinal system (modulated by the gut microbiota) and by cerebral monitoring of these signals through integrative mechanisms based on oscillatory coupling between the gastrointestinal system and the brain. We will study the brain-gut coupling via the simultaneous measurement of the electro-encephalographic and electrogastrography activity, and its relationship to wellbeing. Additionally, using a double-blind, placebo-controlled design, a four-week treatment with probiotics and a gastric awareness training will be used to explore the possible ways via which this coupling might be modulated. In addition to a better understanding of the brain-gut-microbiota regulatory mechanisms, through the inclusion of multilevel measurements spanning Biological, Neurophysiological and Psychological variables, this work aims to contribute to the development of integrative methodological frameworks to assess complex phenomena like human behavior.

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104) Increased functional connectivity in the human reconstructed brain during memory consolidation

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Consolidation of memory is known as the stabilization of newly acquired information in the brain. This process requires reactivation of the neural networks activated during the encoding process allowing the transfer of information to brain sites of long-term storage, and different mechanisms are involved in this phenomenon. Spindles are an essential mechanism for long-term storage in cortical networks. Spindles originate in the thalamus and travel to the neocortex, reaching also the hippocampus. Spindle activity is increased during sleep after learning in those areas involved in encoding [1]

Twenty subjects learned a visual object-location task before going to sleep. The task was associated with an odor, linking it to the content/context of encoding. All participants were presented with the task-related odor during the night. Alternatively, the task-related odor (A) and a sham odor (B, or unrelated to any task) were delivered for 15s alternating with 15s of odor-off condition. We analyzed 129-channel EEG recordings during learning and sleep. Source localization was calculated by anatomical MRI images, co-registered to the EEG electrode positions. Volume sources were computed using dSPM and labeled by the AAL Atlas. Using the reconstructed data, we analyzed changes in the connectivity by coherence measures of the time-series of different brain regions linked to odor A (cue) vs odor B (sham) using the “odor off” period as a baseline. Coherence was calculated in the frequency band of spindle activity (11-15.5Hz) for all trials, and a Wilcoxon test was performed for all subjects in different time periods of the signal.

Results show an increase in the coherence for the Odor condition as compared to the sham condition in the left superior occipital lobe to the left and right thalamus, right fusiform gyrus, left parahippocampus and left hippocampus, a few seconds after the stimulation, suggesting greater functional connectivity between these areas. All these areas have been shown in the past to play an important role in the consolidation process. Our results support the use of source reconstruction techniques to detect and characterize memory reactivations.

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105) Reward magnitude increases learning rate and the activity in value-related brain areas in adolescent

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Introduction:
Adolescence is a developmental stage associated with risky decisión-making. Behaviourally, greater sensitivity to incentives and relatively weak cognitive control have been observed, and may contribute to risky behaviours. Neurobiologically, this is based on the fact that the brain systems underlying learning involving reward and cognitive control systems are in a particularc (dis)balance.

How do cognitive control and reward brain circuits interact during risky decision-making in adolescence? We hypothesized that the change in the magnitude of the reward would generate a change in the learning rate and/or a bias (positive or negative) in the estimation of the value versus the contingency change, influencing the risky decisión-making.

Methods:
Seventeen healthy subjects (10 women, 18-19 years), completed the experimental protocol approved by the Ethics Committee of Universidad del Desarrollo. Subjects participated in two sessions, including a behavioral session and an functional MRI scan session. In both sessions subjects solved a Task associated to risk and learning. During the behavioral session participants played the game on a computer, and during the fMRI, a T1 and a T2* sequences were acquired in a 3T MRI machine.

Results:
Behavioral study: In order to evaluate the learning rate associated to reward sensitivity we adjust the learning rate for each reward amount ($0 $10 $100). We found the higher the reward, the higher the learning rate (rho= 0.3012; p= 0.0485). MRI: In order to evaluate the brain activity associated to reward sensitivity we subtracted the activity of without reward from the different reward amounts. We found a peak activation located in the ventral striatum. Then we explored for the activity related to the difference of reward. We found an activity located in medial posterior parietal cortex and ventromedial prefrontal cortex.

Conclusions:
Our results indicate an increase in the learning rate as the reward increases. This accounts that, as the reward increases subjects become more sensitive to the immediate. Interestingly, this learning rate increase are related to subcortical and cortical areas related to value encoding during decision-making. These activity could be underlying risky decision making during adolescence.

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106) Automated segmentation in the diagnosis of focal cortical dysplasias with magnetic resonance imaging

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Introduction
Focal cortical dysplasias (FCD) are a frequent cause of epilepsy. It has been reported that up to 40% of them cannot be visualized by means of conventional magnetic resonance imaging. The main objective of this work is to evaluate whether the automated brain segmentation is useful for detecting FCD.

Materials and Methods
Through a retrospective, descriptive observational study, 155 patients who underwent surgery, registered in the database of the Advanced Epilepsy Center between the years 2009 and 2016, were reviewed. 20 patients with FCD confirmed by histology and a preoperative segmentation study (with FreeSurfer), with ages ranging from 3 to 43 years (14 men) were analyzed. Three expert neuroradiologists analyzed conventional and advanced MRI imaging with automated segmentation. They were classified into positive and negative concerning the visualization of FCD by consensus.

Results
We defined:
Cortical true thickening: visible increase in cortical thickness as evidenced in FreeSurfer segmentation, defined by visualization of the same cortical thickness in surface segmentation (lines) and volume (color). Cortical pseudothickening: an increase in cortical thickening visualized in volume segmentation (color) which is not represented in surface segmentation (lines). Of the 20 patients evaluated with conventional MRI, 12 were positive for FCD. Of the negative studies for FCD with conventional MRI, 25% were positive when they were analyzed with automated segmentation. In 13 of the 20 patients (38.5%), cortical true thickening was observed and pseudothickening in the rest of patients in the anatomical region of the brain corresponding to the dysplasia.

Conclusion
This work demonstrated that automated brain segmentation helps to increase detection of focal cortical dysplasias that are unable to be visualized in conventional MRI images.

107) Early mechanism of cognitive deficiency in patients with mild cognitive impairment

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Alzheimer´s disease (AD) is the most common neurodegenerative disorder in the world with an incidence projected to be three-times higher in 2050. A transition state described as Mild Cognitive Impairment (MCI) presents with early deficits in the spatial navigation ability as a reflection of damaged hippocampal networks widely reported in AD patients, which induces aberrant patterns of activity in neuronal circuits and Functional Connectivity (FC) alterations. We hypothesized that alterations in long-range FC networks in a navigational task act as early markers of deterioration in AD, and that these alterations constitute part of the early mechanisms in amnestic MCI (aMCI). Using brain activity recordings with EEG and eye movement tracking, we compared 9 aMCI patients and 9 healthy controls while performing a virtual-navigation task. We found that a) there was a significant difference in the electrical brain activity between groups reflected in the analysis of spectral power and FC synchrony at low-frequency bands, b) spatial navigation of the aMCI group was significantly worse than the control group with respect to error rates, latency to the platform, and time without making movements during search of the hidden platform, c) the amplitude of the fixation evoked potentials in the region of interest (occipital electrodes) was significantly lower in the aMCI than the control group and d) as a control, there were no significant differences between groups regarding parameters of ocular behavior (fixations and saccades). Differences in our results suggest they may be a warning of early visual processing difficulties with repercussions on the activation of the cortices involved in the creation of the cognitive map in spatial navigation. Finally, we can conclude that FC may be a good tool to predict progression to AD. Supported by National Fellowship Ph.D., CONICYT 2018, Folio 21180413 (National Commission of Scientific and Technological Research).

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108) Fine sensorimotor coupling hastens encoding processing of working memory

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(Sponsored by Funded By CONICYT-PFCHA 21150153 And ICM P09-015-F)

Working memory (WM) has been classically studied in a way that requires subjects to passively wait for the stimulus onset. Nevertheless, in natural behavior, encoding in WM is typically accomplished using motor acts to select relevant-to-task sensory information. We propose that the sensorimotor coupling during the encoding stage in WM beneficiates WM processing, which may be evidenced by the enhancement of the neural activity related to encoding. Twenty-five subjects participated in a WM task with 3 encoding conditions: coupled, where participants pressed a button for the stimuli appearance; decoupled where there was a delay between the button pressing and the stimuli presentation, and passive in which the stimuli appeared automatically.

Behavioral results show a statistically significant improvement of performance in the coupled condition versus the other two conditions and significantly worse performance of the passive condition with respect to the other two. Event-Related Potentials (ERPs) results show shortened latencies for N100 in coupled condition, while no effects over its amplitude, nor the amplitude or latency of the P300 component. However, this N100 latency modulation was not related to behavioral enhancement.

Our results suggest that sensorimotor coupling contributes to the mechanisms of the working memory, while fine temporal coupling being a critical feature of the sensorimotor modulation. Our results also indicate that fine temporal sensorimotor coupling hastens early visual processing during WM encoding, in spite, this modulation doesn't appear to explain the performance improvement. Our study seems to endorse previous findings that had proven similar effects on other cognitive processes such as perception, attention, time perception and predictions, suggesting that sensorimotor coupling could be a global mechanism of precise temporal modulation.

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109) High density EEG-assisted identification of Targeted Memory Reactivation in cortical and subcortical regions of the human source-reconstructed brain

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Memory reactivation (MR) refers to the consolidation of memories by reactivation of neural networks implicated in information encoding[1,2]. Studies in rodents show that MR predominantly occurs during Slow Wave Sleep and may implicate specific electrophysiological wave patterns such as Slow Oscillations (SO) and coupled thalamocortical sleep spindles[3–5]. In humans, MR has been identified by scalp EEG[6], but has however never been assigned to discrete brain areas. Here, we compare neural patterns from scalp EEG and reconstructed brain sources in an experiment of cue-mediated MR (Targeted Memory Reactivation, TMR). 20 subjects learned 2 different versions of an object-location task before sleep during 2 nights. Each task was associated with an odor (A), linking it to the content/context of encoding. Two hours before the task, subjects performed a finger-tapping task linked to a different odor (B). All participants were presented with odor A during one and with odor B the other night in a randomized way. Alternatively, task-related odor (A or B) and placebo odor (C, non-related to any task) was delivered during 15s alternating with 15s of an odorless vehicle (alternating time series of 30s). We recorded 129-channel EEG during learning and sleep. Source localization was informed by anatomical T1-weighted MRI co-registered to the EEG electrode positions. Volume sources were computed by dSPM[7] and labeled by the AAL Atlas. In this study, we analyzed changes in sleep spindle activity linked to odor A (cue) vs odor C (sham). Time series analysis revealed a significant decrease in spindle density after both sham and cue presentation in thalamus source and C3 channel measures. However, when spindle activity of the thalamus was phase-coupled to SO activity of the prefrontal cortex[5,8], this decrease was mediated only by cue and absent after sham presentation. Furthermore, no changes were identifiable in phase-coupled channel measures. This suggests a crucial need for source reconstruction in the context of TMR in humans. Our results suggest that TMR acts via changes in spindle density coupled with cortical SO.

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