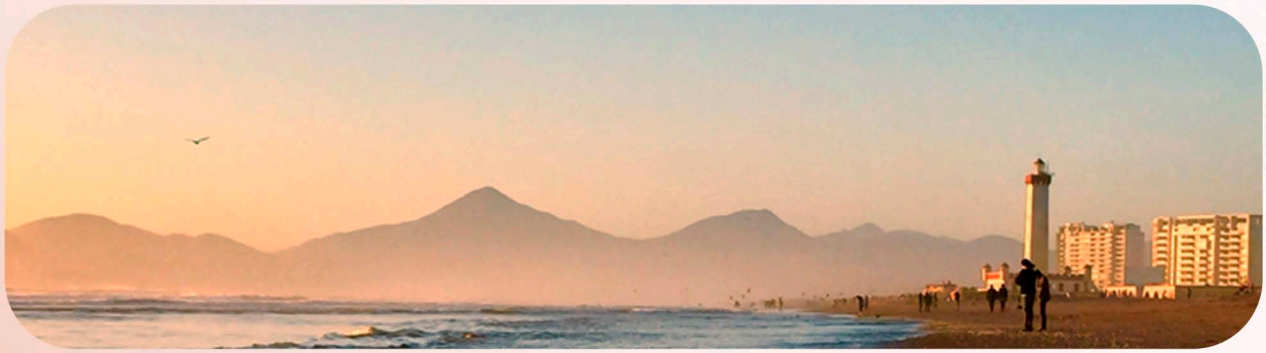
Sociedad Chilena de Neurociencia

XIX Reunión Anual Sociedad Chilena de Neurociencia



Hotel Club la Serena

16 al 18 de octubre 2023

XIX Annual Meeting
Sociedad Chilena de Neurociencia
October 16-18, 2023

	Monday 16T	uesday 17W	ednesday 18
9:00 - 11:00	**Registration**	S3: New Insights in intracellular traffic in Neurons *Elqui 1* S4: Non-invasive brain stimulation as a tool for the search of human behavior neural correlates *Elqui 2*	S5: Neuroscience in Drosophila- an insect brain to study the human brain *Elqui1* S6: Neuronal Circuits and Behavior *Elqui2*
11:00 - 11:30		***Coffe break***	
11:30 - 12:30		Mesa Redonda ¿Cómo divulgar la neurociencia? *Elqui 3*	PL3: Relevance of agonist promiscuity among sensory TRP channels: Redundancy or wide dynamic range? Dr. Karel Talavera *Elqui 3*
12:30 -13:30		Sponsors' Talk: El futuro ahora. El potencial de los biomarcadores neurológicos en el diagnóstico de las demencias. Genexpress *Elqui 1*	Asamblea de socios *Elqui 2*
13:30 -14:00			Sponsors' Talk RWD *Elqui1*
14:00 -15:30	***Lunch Break***		
15:30 - 17:30	S1: Ion channels in pain neurophysiology *Elqui 1* S2: Role of non-neuronal cells on CNS function and repair *Elqui 2*	Young Neuroscientists Symposium (YNS) *Elqui 3*	Oral Communications I *Elqui1* Oral Communications II *Elqui2*
17:30 -18:00	***Coffee break***		
18:00 - 19:00	PL1: The corticostriatal system in health and disease Dr. Per Petersson *Elqui3*	PL2: Cell to cell communication mediates glioblastoma progression Dr. Sergio Casas *Elqui 3*	Mesas de trabajo *Elqui 3*
19:00 - 20:00	Poster Session I	Poster Session II	Best Poster and Oral Communication Award Ceremony *Elqui 3*
20:00 - 21:00			Tribute to Dr. Christian Bonansco Dr. Marco Fuenzalida *Elqui 3*
21:00	Welcome cocktail		Farewell cocktail

AUSPICIADORES

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Plenary Lectures

The corticostriatal system in health and disease

Per Petersson[1]

(1) Umeå University, Integrative Medical Biology, Medicine, Johan Bures v. 12, Umeå, Sweden

The cerebral cortex, together with the basal ganglia, have an important role in the regulation of our behavior, by controlling fundamental functions such as the selection and initiation of specific actions, as well as motor learning. Many of the network computations needed to carry out these tasks are thought to be mediated by the corticostriatal system – that is, neurons located in different cortical areas that project convergently to the striatum, the input layer of the basal ganglia. It is therefore not surprising that neurophysiological recordings from both patients and animal models of diseases affecting the cortico-basal ganglia system have revealed abnormal physiological signatures that are strongly associated with specific symptoms within both the motor and non-motor domain. These aberrant brain activity patterns can potentially inform us on disease mechanisms and are already being used as real-time biomarkers of circuit dysfunctions to help guiding the development of new treatments.

In this lecture, data from a few recent studies will be presented illustrating the involvement of corticostriatal circuits in the control of both spontaneous and learned motor behaviors, in the healthy brain. In the second part, the pathophysiological perspective will be in focus, where recent results suggesting shared mechanisms underlying circuit dysfunctions in sensorimotor and cognitive-limbic aspects of the corticostriatal system will be discussed.

Financing: The study was supported by grants from the Kempe Foundation, Insamlingsstiftelserna, Oskarfonden, Umeå University, The Swedish Brain Foundation, Vetenskapsrådet (VR) Grant 2018-02717 and Grant 2021-01769, Olle Engkvist Foundation, The Parkinson Foundation, Kockska Foundation, Hedlund Foundation, Åhlén Foundation, Promobilia, LU Innovation, Wenner-Gren Foundation, Royal Physiological Society in Lund.

Cell to cell communication mediates glioblastoma progression

Sergio Casas-Tintó[1]

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Glioblastoma (GB) is the most aggressive, lethal, and frequent primary brain tumor. It originates from glial cells and is characterized by rapid expansion through infiltration. We have studied how GB cells interact with the microenvironment and healthy surrounding tissues, mostly neurons and vessels. GB cells project tumor microtubes (TMs) that contact with neurons, and exchange signaling molecules related to Wingless/WNT, JNK, Insulin, or Neuroligin-3 pathways. This cell-to-cell communication promotes GB expansion and neurodegeneration. Moreover, healthy neurons form glutamatergic functional synapses with GB cells which facilitate GB expansion and premature death. Targeting signaling and synaptic components of GB progression may become a suitable strategy against glioblastoma. In a Drosophila GB model, we have determined the post-synaptic nature of GB cells with respect to neurons, and the contribution of post-synaptic genes expressed in GB cells to tumor progression. In addition, we document the presence of intratumoral synapses between GB cells, and the functional contribution of pre-synaptic genes to GB calcium-dependent activity and expansion. Finally, we explore the relevance of synaptic genes in GB cells to the lifespan reduction caused by GB advance. Our results indicate that both presynaptic and postsynaptic proteins play a role in GB progression and lethality

Relevance of agonist promiscuity among sensory TRP channels: Redundancy or wide dynamic range?

Karel Talavera Perez[1]

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Since their original cloning from the fruit fly, transient receptor potential (TRP) channels have received great attention due to their ubiquitous expression, capability to permeate Ca^{2+} and other cations, and consequent roles as regulators of Ca^{2+} signaling and membrane potential. Several TRP channels are notorious for been activated by thermal, chemical and mechanical stimuli. It is intriguing, however, that many of them can be activated by the same stimuli, for instance, heat, cold, bacterial endotoxins and multiple chemical compounds functioning as plant defensive traits. It has been recently proposed that several heat-activated TRP channels have redundant functions in the detection of heat. We argue, however, that this idea is inconsistent with the rules of natural selection and evolution, and that other principles underlie such agonist promiscuity. Based on the thermodynamic analysis of TRP channel gating, and supported by a novel application of Shannon Information Theory, we suggest that the strong sensitivities to thermal, mechanical and chemical stimuli are in part driven by the low sensitivity of these channels to membrane potential. By discussing several examples of TRP channel activation mechanisms, we provide evidence that agonist promiscuity does not serve as mechanism of redundancy, but rather as an enhancement of the dynamic range of stimulus detection in sensory cells. Our analyses may serve to stimulate future studies on the molecular evolution of TRP channels, which might help in the quest of the understanding of the pathophysiological roles of these fascinating and still intriguing ion channels.

Financing: FWO Flanders and Research Council KU Leuven

SYMPOSIUM

SYMPOSIUM 1

Ion channels in pain neurophysiology

Chair: Rodolfo Madrid and María Pertusa

Cdk5-mediated regulation of nociceptive channels in sensory ganglia

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(2) Millennium Nucleus for the Study of Pain (MiNuSPain), Santiago, Chile

Cyclin-dependent kinase 5 (Cdk5) plays an important role in several physiological and pathological processes both in the central and peripheral nervous systems, including functions in trigeminal ganglia (TG) and dorsal root ganglia (DRG). We have demonstrated that Cdk5 is a key kinase implicate in orofacial pain signaling pathways. Cdk5 phosphorylates TRPV1 and P2X2 ion channels, expressed in trigeminal sensory neurons, which in turn causes peripheral sensitization. Cdk5-mediated TRPV1 and P2X2 phosphorylation increase Ca^{2+} influx and pain perception in mice. On the other hand, Cdk5 expression, regulation, localization, and function in neurons of the nodose ganglia of the vagus nerve has not been studied. Therefore, we studied the expression and localization of Cdk5 and its activators p35 and p39 in nodose ganglia neurons from mice and rats. In addition, we analyzed colocalization of Cdk5 with some of its possible substrates, such as TRPV1 and P2X2 channels. Finally, we analyzed Cdk5 function in nodose ganglia through isolated ganglia electrophysiological recordings and functional baroreflex assays in loss and gain of function models for Cdk5. Our results show that Cdk5 is present and active in murine nodose ganglia and indicate its kinase activity can functionally modulate baroreflex activity.

Financing: Fondecyt 1191552. Millennium Nucleus for the Study of Pain (MiNuSPain) NCN19_038, Santiago, Chile

Role of Kv1 and TRPM8 channels in cold allodynia.

Rodolfo Madrid[1,2,3]

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(2) Millennium Nucleus of Ion Channel-Associated Diseases - MiNICAD, Santiago, Chile
(3) Millennium Nucleus for the Study of Pain - MiNuSPain, Santiago, Chile

Painful hypersensitivity to innocuous cold, or cold allodynia, is one of the most frequent and debilitating symptoms of neuropathic pain resulting from peripheral nerve injury. Their clinical manifestations vary among individual patients and somatosensory territories, and despite the advances in the study of the mechanisms underlying this often-invalidating sensory alteration, their molecular and cellular bases remain poorly understood. In the trigeminal and spinal somatosensory systems, cold thermoreceptors and nociceptors are the primary sensory neurons responsible for the detection of temperature drops. Cold transduction and cold-induced firing in these neurons result from the concerted action of different background, transduction, and voltage-gated ion channels in specific subpopulations of primary afferents. Several of these molecular entities have been proposed as important elements in neuropathic cold pain. In this symposium, we will present our results supporting the idea that damage-triggered cold allodynia is mainly due to a functional unbalance between the cold-activated channel TRPM8 and Shaker-like Kv1 channels responsible for the brake K^+ current I_{KD}, with a key involvement of these two functionally counteracting molecular entities whose contribution could be specific on different somatosensory territories. This unbalance increases cold sensitivity in high-threshold cold thermoreceptors and induces the recruitment of silent former cold-insensitive fibers signaling pain, providing a general molecular and neural mechanism for cold allodynia in response to peripheral nerve damage. Financing: Supported by Millennium Nucleus for the Study of Pain (MiNuSPain), VRIIC-USACH 021843MM, and Millennium Nucleus of Ion Channel-Associated Diseases (MiNICAD).

Modulation of glycinergic neurotransmission and its relevance in chronic pain

Gonzalo E. Yévenes[1,3], Victoria P. San Martin[1,3], Cesar O. Lara[1,3], Ana M. Marileo[1,3], Omayra Contreras[1,3], Cecilia Bouzat[2], Carlos F. Burgos[1], Patricio Castro[1], Jorge Fuentealba[1], Luis G. Aguayo[1], Gustavo Moraga-Cid[1]

(1) Universidad de Concepción, Departamento de Fisiología, Facultad de Ciencias Biológicas, Concepción, Chile
(2) Universidad Nacional del Sur-Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Departamento de Biología, Bioquímica y Farmacia, Instituto de Investigaciones Bioquímicas de Bahía Blanca, Bahía Blanca, Argentina
(3) Millennium Nucleus for the Study of Pain (MiNuSPain), Santiago, Chile

Glycinergic neurotransmission contributes to neuronal inhibition through fast synaptic inhibition, activation of tonic currents, and presynaptic modulation. These processes are key for essential physiological functions, such as respiratory rhythm, motor control and sensory processing. In addition, diverse alterations in molecular elements of the glycinergic neurotransmission are common features of several chronic pain states. Interestingly, evidence from our group and others has shown that positive allosteric modulators (PAMs) of glycine receptors (GlyRs) exhibit analgesic effects on chronic pain models. Despite its relevance, a complete understanding of the relevance of the glycinergic system in chronic pain is still missing, and moreover, the pharmacological modulation of glycinergic neurotransmission has not yet been translated into clinical applications. Our recent data show that GlyR subtypes are differentially modulated by diverse compounds, including synthetic molecules and natural alkaloids. We found that these compounds modulate GlyRs through different mechanisms, involving distinct binding modalities and allosteric pathways. Additionally, recent results using genetically-modified mice suggest that GlyR subtypes contribute asymmetrically to the maintenance of chronic pain. Work in progress will contribute to establish a compelling view of glycinergic neurotransmission alterations in chronic pain, paving the path towards advanced biomedical tools.

Financing: Supported by ANID-FONDECYT 1211082, ANID-FONDECYT 1211095, ANID-FONDECYT 11221211, IBRO Collaborative Research Grants, and by the Millennium Nucleus for the Study of Pain (MiNuSPain). MiNuSPain is supported by the Millennium Scientific Initiative NCN19_038 of the Ministry of Science, Technology, Knowledge and Innovation, Chile.

Role of subthreshold membrane potential instabilities in sensory transduction

Enrique Velasco[1], Michael Mazar[3], Rachely Butterman[3], Victor M. Meseguer[2], Juana Gallar[2], Julio L. Alvarez[1], Alexander Binshtok[3], **Karel Talavera**[1]

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(2) Instituto de Neurociencias, San Juan de Alicante, Spain
(3) The Hebrew University of Jerusalem, Jerusalem, Israel

Rather than being electrically quiescent while not firing action potentials, peripheral sensory neurons can display marked subthreshold membrane potential instabilities (SMPIs), but the relevance for physiological sensation and molecular bases of this phenomenon remain unknown (Velasco et al. Pain, 2022). Here, we aimed at addressing this issue by analyzing whole-cell current-clamp recordings performed in primary cultured mouse trigeminal (TG) neurons. We found that small diameter neurons recorded displayed SMPI activity in the shape of Membrane Potential Transients (MPTs). The frequency, amplitude and rates of upstroke and repolarization of MPTs were increased by membrane depolarization. Morphological analyses of the MPTs and of the initial depolarizing phase of action potentials (AP) revealed that larger and faster MPTs precede AP firing. This was confirmed by a regression analysis showing that the maximal rate of depolarization and amplitude of the MPTs strongly predict subsequent AP firing, following a Boltzmann dependency. MPT activity was also enhanced by the application of heat, cold, capsaicin and menthol, via their depolarizing effect on the resting membrane potential. MPT activity was reduced by application of 200 µM TTX and in neurons isolated from $Na_V1.9$ knockout mice. We hereby identify, for the first time, a molecular determinant of the trigger of MPTs and demonstrate a causal relationship between MPTs and AP firing upon exogenous stimulation of sensory neurons. These findings unveil MPTs as crucial regulators of peripheral sensory processing, with possible implications in pathological conditions featuring altered activity of $Na_V1.9$ channels.

Financing: FWO Flanders and Research Council KU Leuven

SYMPOSIUM 2

Role of non-neuronal cells on CNS function and repair

Chair: Fernando Ortíz

Microglia-Neuron interaction in aging and its relevance for neurodegenerative diseases.

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Age-related changes in glial cell activation and neuroinflammation are involved in the pathophysiology of neurodegenerative diseases. We propose that changes on neuron-microglia regulatory crosstalk in aging participate in the regulation of glial cells cytotoxicity. Those changes affect glial cell activation and cell signaling secondary to inflammatory and regulatory cytokines. They depend on multiple factors, including transforming growth factor (TGFβ) and Scavenger Receptor A (SRA) regulation of glial cell activation, and Fractalkine/CX3CR1 involved in the regulation of microglia by neurons. Our results show that age-related changes result in the modification of glial cells regulation Here, we will discuss age-dependent changes of various pathways in the brain of wild type (WT) and an inflammatory mouse model (knockout for SRA, SRA-KO). WT and SRA-KO mice of 3-6-, 12- and 20-month-old were analyzed. To assess the effect of inflammation, mice were administered intraperitoneal 1 mg/kg of LPS or vehicle. 2-to-24 hours later, various receptors were analyzed by qRT-PCR and western blot, whereas the distribution of receptors and signaling pathways activation were assessed by immunohistochemistry. We observed that changes on TGFβ, activation of inflammatory signaling pathways, SRA and fractalkine were affected by aging, even in the absence of exogenous inflammation. Several changes are already observed at 12 months, including a 3-fold increase of Fractalkine compared with that of young mice, with predominance of soluble isoforms. Our findings suggest that aging favors the generation of soluble (cleaved) forms of Fractalkine, promoting microglial activation and a neuroinflammatory environment.

Financing: Proyecto FONDECYT 1221028, ANID REDES 190187

Alcohol consumption and astroglial dysfunction: Involvement of large-pore channels

Juan Andrés Orellana[1]

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Multiple studies have demonstrated that ethanol consumption alters brain function and cognition. Nevertheless, the mechanisms underlying this phenomenon remain poorly understood. Hemichannels and pannexons serve as ionic and molecular exchange conduits between the cytoplasm and extracellular milieu, allowing the release of various paracrine substances, such as ATP, D-serine, and glutamate, and the entry of other substances, such as Ca^{2+} and glucose. The persistent and exacerbated opening of hemichannels and pannexons have been associated with the progression of several brain diseases. Here, we evaluated whether ethanol affects the activity of astrocyte hemichannels and pannexons and the possible repercussions of this phenomenon on several aspects of astroglial function. Ethanol enhanced the opening of connexin 43 (Cx43) hemichannels and pannexin-1 (Panx1) channels in cultured mouse cortical astrocytes. This response was a time and concentration-dependent phenomenon relying on Toll-like receptor 4 (TLR-4), IL-1β/TNF-α, the p38 MAP kinase, the inducible nitric oxide (NO) synthase (iNOS), cytoplasmic Ca^{2+} ($[Ca^{2+}]_i$) and purinergic and glutamatergic signaling. Notably, the ethanol-induced opening of hemichannels and pannexons resulted in alterations in $[Ca^{2+}]_i$ dynamics, gliotransmitter release, and mitochondrial function. Interestingly, in vivo ethanol administration augmented the opening of Cx43 hemichannels and Panx1 channels in hippocampal astrocytes from rat hippocampus. Importantly, ethanol-induced Cx43 hemichannel and Panx1 channel activity was correlated with increased levels of IL-1β, TNF-α, IL-6 in the hippocampus, as well as with profound alterations in astrocyte arbor complexity. Thus, we propose that uncontrolled opening of astrocyte hemichannels/pannexons may contribute to astrocyte dysfunction and likely to neurotoxicity caused by alcohol consumption.Financing: FONDECYT 1210375

Role of meningeal lymphatic vasculature in homeostasis and disease of the central nervous system

Noelia Escobedo[1]

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Major advancements in neurobiology include the recent (re)discovery of a lymphatic vasculature within the meninges. Meningeal lymphatic vessels (mLV) are responsible for the drainage of immune cells, macromolecules, and fluid from the central nervous system (CNS) into the deep cervical lymph nodes (dCLNs). Impairment or malfunction of mLV may significantly impact on cerebrospinal fluid (CSF) clearance and exacerbate the buildup of protein aggregates. Yet, the contribution of defective mLV in neurodegenerative diseases is largely unexplored. The lysosomal storage diseases (LSDs), comprise a large group of pediatric neurodegenerative disorders caused by deficiency of lysosomal enzymes and associated with complex neurological phenotypes; however, the contribution of mLV to neurodegenerative LSDs, or the possible link between lysosomal function and mLV has not yet been explored. Here, we identify the sialidase neuraminidase 1 (Neu1) as the first lysosomal enzyme involved in the maintenance and preservation of mLV structure and function. In the mouse model of sialidosis, an LSD triggered by a deficiency of Neu1 ($Neu1^{-/-}$), we observed morphological defects of the mLV, characterized by excessive ectopic branching and increased area within the meninge; CSF accumulation in the cranium; and poor drainage of fluid into the dCLNs. Moreover, $Neu1^{-/-}$ mice display early infiltration of immune cells in their meninges prior to mLV morphological changes and are maintained throughout the course of the disease, contributing to the inflammation of the CNS. Our findings highlight the importance of lysosomal Neu1 in maintaining the mLV and therefore the proper CSF drainage and CNS homeostasis.

Financing: FONDECYT 1201562 Acknowledgments: FONDECYT 1201562 y Proyecto FONDEQUIP-ANID EQM200122

The Vascular Niche During Remyelination in Multiple Sclerosis – Friend or Foe?

Francisco J. Rivera Gómez-Barris[1,2,3]

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Multiple sclerosis (MS) is an autoimmune neuroinflammatory demyelinating disease of the central nervous system (CNS) that affects about 2.5 million people worldwide. In response to demyelination, oligodendrocyte progenitor cells (OPCs) proliferate, migrate, and differentiate into newly myelinating oligodendrocytes. Although remyelination represents a robust regenerative response to myelin damage, it extensively fails in MS and current therapies lack repair activities. Thus, revealing unknown molecular / cellular cues that control myelin regeneration and identifying inhibitory signals for remyelination represent two essential milestones in MS research. Using different animal models combined with omics strategies and several in vitro approaches, our research group aims to determine the role of the vascular niche in myelin regeneration. In this regard, our studies have identified CNS-resident perivascular cells (PVCs) and circulating platelets as potent modulators of OPC function during remyelination. Also, abnormalities in these cells contribute to remyelination failure. Overall, these studies positioned PVCs and platelets as potential targets for the developing of regenerative therapies for MS treatment.

Financing: Agencia Nacional de Investigación y Desarrollo (ANID, Chile)-FONDECYT Program Regular Grant Number 1201706 and 1161787, ANID-PCI Program Grant N° REDES170233 and N° REDES180139, ANID-National Doctoral Fellowships. PROFI Funding of the Academy of Finland and the University of Helsinki.

Acknowledgments: Special acknowledgements to the Comité Ético y Científico del Servicio de Salud de Valdivia (CEC-SVS) for ethical guide and approval (ORD Nº 510).

SYMPOSIUM 3

New Insights in intracellular traffic in Neurons

Chair: María Paz Marzolo

ApoER2 is new a Cargo for the Adaptor Protein Complex AP-4: Implications for Reelin Signaling in neurons.

Mario O. Caracci[1], Héctor Pizarro[1], Carlos Alarcón-Godoy[1], Luz M. Fuentealba[1], Pamela Farfán[1], Raffaella De Pace[2], Natacha Santibañez[3], Viviana A. Cavieres[4], Tammy P. Pástor[4], Juan S. Bonifacino[2], Gonzalo A. Mardones[4,*] **María-Paz Marzolo[1]**

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Adaptor protein complex 4 (AP-4) is a heterotetrameric complex that promotes protein export from the trans-Golgi network. Mutations in each of the AP-4 subunits cause a complicated form of Hereditary Spastic Paraplegia (HSP). We describe that ApoER2, is a cargo of the AP-4 complex. identifying the motif ISSF/Y within the ApoER2 cytosolic domain as necessary for interaction with the canonical signal-binding pocket of the μ4 subunit of AP-4. Hippocampal neurons from Ap4e1-KO mice and AP4M1-KO human iPSC-derived cortical i3Neurons exhibit reduced ApoER2 protein expression. Analyses of biosynthetic transport of ApoER2 reveal differential post-Golgi trafficking of the receptor, with lower axonal distribution in KO compared to wild-type neurons, indicating that the interaction of ApoER2 with regulated the axonal localization signaling in mouse hippocampal and human cortical KO neurons show a reduction of Reelin-induced ERK phosphorylation, CREB activation, and Golgi deployment. Altogether, this work establishes ApoER2 as a novel cargo of the AP-4 complex, suggesting that defects in the trafficking of this receptor and in the Reelin signaling pathway could contribute to the pathogenesis of HSP caused by mutations in AP-4 subunits.

Funding: Fondecyt 1200383

Taking out the trash: the roles of Rab7 in dendritic proteostasis

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Rab7 is one of the critical regulators of endosomal trafficking in all cells, including neurons. Consequently, Rab7 is involved in regulating the decision to recycle or degrade which affects proteostasis but also signaling from important classes of signaling receptors which signal from endosomes. Rab7 mutants are genetically linked to a human disease, Charcot Marie Tooth disease CMT2B which presents with peripheral axonopathy but most other cell types in the body are not known to be affected. This points to a particular vulnerability of neurons to disturbance of Rab7-mediated trafficking. The roles of Rab7 in neuronal trafficking are still being illuminated. We are using multiple approaches to determine the regulatory nodes for Rab7 with a particular focus on dendrites. We are finding that Rab7 plays measurable roles in early endosome maturation to late endosomes, motility of late endosomes towards the soma, and degradation of dendritic cargos. Acidification and degradative capacity per se are not impaired. Our data point to a critical role of Rab7 upstream of fusion with lysosomes.

Cellular and molecular mechanism regulating neuronal plasticity by Brain-derived neurotrophic factor (BDNF) signaling endosomes

Francisca Bronfman[1], Alejandro Aguirre[1], Reynaldo Tiburcio-Felix[1], Xavier Valero[1]

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The brain-derived neurotrophic factor (BDNF) and its receptor TrkB (tropomyosin kinase receptor B) control the connectivity of different neuronal networks in the central nervous system (CNS) by regulating the activation of signaling pathways leading to transcriptional regulation and translation of proteins. After being bound by BDNF, TrkB is endocytosed into endosomes and continues signaling within the cell soma, dendrites, and axons in signaling endosomes. Our recent findings demonstrated that dynein-dependent BDNF-TrkB-containing endosome transport in axons is required for long-distance induction of dendritic growth. On the one hand, axonal signaling endosomes increase PLC-gamma in axons, allowing signaling endosome transport. On the other hand, CREB and mTOR kinase activity in the cell body and the activity of both proteins was required for general protein translation and the expression of Arc. Arc is a plasticity-associated gene, indicating a role for BDNF-TrkB axonal signaling endosomes in coordinating the transcription and translation of genes whose products contribute to neuronal plasticity.

The family of monomeric Rab GTPases is the principal regulator of membrane trafficking and governs the intracellular transport of different organelles. Membrane-bound Rabs bind varying effectors, including microtubule-based molecular motors, participating in membrane recognition and fusion steps. Our lab has shown a bidirectional relation between BDNF signaling and RabGTPas controlling the early-recycling endocytic pathways (Rab5 and Rab11, respectively) to allow membrane transport and neuronal plasticity. This talk will present an integrated view of the cellular mechanism controlling BDNF neuronal plasticity in SNC neurons.

Palabras claves; BDNF, signaling endosomes, dynein, RabGTPases, signaling pathways, neuronal plasticity

Financing: Fondecyt Nº1221203

High temporal frequency light transmission in the retina is mediated by ON and OFF bipolar cells and requires FAT3 signaling to properly traffic glutamate receptors to the synapse

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Vision is initiated by the reception of light by photoreceptors, which is further processed via parallel retinal circuits. Proper circuit organization depends on the multi-functional tissue polarity protein, FAT3. Previous studies showed that retinal lamination is severely disrupted in Fat3 mutant mice. Here we investigated Fat3 mutant mice for physiological phenotypes, and found decreases in physiological and perceptual responses to high frequency flashes. These defects did not correlate with abnormal amacrine cell wiring, but pointed to a role for FAT3 in bipolar cells. Indeed, similar deficits were observed in mice lacking the bipolar cell glutamate receptors, GRIK1 (OFF-bipolar cells) and GRM6 (ON-bipolar cells). Mechanistically, FAT3 binds to the synaptic protein PTPs and is required to localize GRIK1 to OFF-cone bipolar cell synapses with cone photoreceptors. Grik1 mRNA is not significantly affected in Fat3 mutants, pointing to a role for FAT3 in the trafficking of GRIK1 protein to the ribbon synapse. These findings expand the repertoire of FAT3 functions and reveal the importance of both ON and OFF bipolar cells for high frequency light transmission.

Financing: Harvard Medical School, NIH

Acknowledgments: Co-authors: Sean K. Wang, Sarina Patel, Vladimir J. Kefalov, Lisa V. Goodrich, Constance L. Cepko, Yunlu Xue

SYMPOSIUM 4

Non-invasive brain stimulation as a tool for the search of human behavior neural correlates

Chair: Juan José Mariman

Uses of frequency-specific non-invasive brain stimulation of visuo-attentional networks to modulate conscious perception: From causal cognitive anatomy to visual rehabilitation and back?

Antoni Valero-Cabré MD PhD[1,2,3], Chloé Stengel PhD[1], Marine Vernet PhD[1], Romain Quentin PhD[1], Xavier Corominas-Teruel MSc[1], Alexia Potet MD[1], Monica Toba PhD[1]

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[2] Cognitive Neuroscience and Information Technology. Research Program, Open University of Catalonia (UOC), Barcelona, Spain.
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Abstract
For the last 20 years, non-invasive stimulation approaches (NIBS), notably Transcranial Magnetic Stimulation (TMS) and Current Stimulation (tCS) have gained popularity to causally characterize anatomical and neurophysiological features subtending cognitive contributions. In humans. On such basis, therapeutic strategies to rehabilitate cognitive dysfunction following brain damage have emerged. Here I will present strengths and limitations of the most popular NIBS used today, to then highlight the key outcomes of a series of studies from our lab aimed at causally maping and characterizing anatomical and neurophysiological features of the dorsal fronto-parietal attentional networks involved in the modulation of visual perception. To this end, first, I will show evidence of frequency-specific high beta (30 Hz) modulation by TMS of the right and left Frontal Eye Fields (FEF), a key region of the dorsal attention network and its facilitatory effects on visual sensitivity (d') but not criterion (c). Second, I will provide EEG proof of such effects as being causally related to the local entrainment of frontal high-beta activity and fronto-parietal synchronization at this same frequency, mediated by the superior longitudinal fasciculus. Third, I will highlight the complexity of such coding in other regions, such as the left FEF by showing the modulatory effects exerted by the desynchronization of this region with noisy TMS patterns. To conclude, I will present preliminary data from an ongoing cross-over double-blind pre-clinical trial assessing the use of Transcranial Alternating Current Stimulation (tACS) to improve visual perception in stroke patients with hemianopia by synchronizing attentional networks.

Acknowledgements
The activities of the laboratory of Dr. Valero-Cabré at the ICM CNRS UMR 7225 have been supported by research grants IHU-A-ICM-Translationnel, Agence National de la Recherche (ANR) FLAG-ERA JTC 2017 'CAUSALTOMICS', and ANR APG 'OSCILLOSCOPUS', PHRC Regional 'NEGLECT', PHRC National 'STIM-SD' and the Fondation Recherche Alzheimer (FRA). The authors thank the FRA foundation for logistic and equipment support and the Naturalia & Biologia Foundation for financial assistance for traveling and attendance to meetings.

Effects of tDCS In Neural Markers In People With Moderate To Severe Traumatic Brain Injury.

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Psychomotor slowness, attention-related disorders, and memory failure are among the most common complaints reported by people suffering chronically from moderate to severe traumatic brain injury (CMS-TBI) and their support networks. Impairment in anticipatory control has been proposed as a central aspect of the psychomotor slowness to explain the difficulty of the subjects to implement an expected timing in the sensory-motor response. Under the predictive coding framework, the ability to anticipate events depends on the capacity to generate predictions at successive hierarchical levels and can be explored through neurophysiological correlates of prediction error signals. Event-related potentials (ERP) allow us to dissect at least three hierarchical levels of prediction error signals: the mismatch negativity (MMN; low-level), the P3a (intermediate level), and the P3b (high-level). On the other side, previous reports have shown that non-invasive brain stimulation over prefrontal areas has a reduced impact on improving cognitive and motor performance. The purpose of our work is to determine if CMS-TBI subjects have disturbances to generate high-level top-down predictions and to explore if these disturbances are modulated through temporary incrementation of neural excitability induced by external, non-invasive neuromodulation.

Influencing neural oscillations through alternating electrical stimulation, a pathway to understanding motor control in health and disease

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The control of movement demands the recruitment of neural structures distributed throughout the nervous system, dynamically configuring neural networks in which both cortical and subcortical regions are involved. The coordination of these brain regions is essential for optimal functioning. It has been suggested that neuronal oscillations can serve as an effective communication mechanism for local and long-distance neural networks. However, its role in various processes of motor control, both in normal states and after neurological injury, remains partially understood. Transcranial electrical stimulation proves to be a valuable tool for modulating neuronal activity. Specifically, alternating stimulation (tACS) at specific frequencies enables the modulation of brain oscillatory activity across a wide range of brain rhythms. In this presentation, we will review the accumulated evidence regarding the use of tACS to entrain brain activity in rhythms associated with motor control, its behavioral and electrophysiological effects, as well as the potential and prospects for its application in studying the neuronal correlates of behavior and its therapeutic utility. In doing so, we will discuss the causal relationships of oscillatory processes in the functioning of the nervous system and the possibility of targeting neural oscillations through tACS to influence human behavior.

Unveiling Cognitive Pathways: Integrating Non-Invasive Brain Stimulation, Computational Modeling, and Brain Activity Measurements for Understanding Behavior

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Non-invasive brain stimulation (NIBS) has emerged as a powerful tool for establishing causality between cerebral processes and behavior. However, interpreting such interventions' effects on behavior is not always straightforward. To gain valuable insights into the underlying cognitive mechanisms, it is crucial to formulate and test hypotheses related to these mechanisms. In this presentation, we will showcase experiments conducted in our laboratory that exemplify an experimental approach grounded in assessing cognitive computational mechanisms. Through the synergistic employment of NIBS, computational cognitive modeling, and measurements of electrical and metabolic brain activity, we can understand the effects of brain stimulation on behavior. Our multidimensional framework holds the promise of unveiling specific pathways that forge connections between the brain and behavior and presents a potential bridge between theoretical insights and practical clinical applications. By identifying specific relationships between brain activity and behavior, we can potentially develop targeted interventions for neurological and psychiatric disorders.

SYMPOSIUM 5

Neuroscience in Drosophila- an insect brain to study the human brain

Chair: Jimena Sierralta

Transglutaminase and histone dopaminylation. Is it time for us to fly?

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Histone aminylation (H3Q5Aminyl) is a recently described post-translational modification (PTM) involving the covalent union between an amine (dopamine or serotonin), and glutamine 5 in histone H3. This reaction is catalyzed by the enzyme transglutaminase 2 (TGM2). Histone serotonylation (H3Q5Ser) is conserved throughout evolution, so it is detected in vertebrates and invertebrates including Drosophila melanogaster. It has been associated to neuronal differentiation. On the other hand, histone dopaminylation (H3Q5Dop) has been only reported in brains of rats and humans and has been linked to addictive behaviors.

Thus, the in vivo roles of H3Q5Aminyl are still not fully understood. It is also unclear whether H3Q5Aminyl is responsive to manipulations that affect amine production and/or signaling, or TG activity. Additionally, it is not known how H3Q5Dop affect gene expression.

Here we advanced on some of these issues in Drosophila. Our results support differential localization of these PTMs in fly brain regions. The detection of H3Q5Aminyl in Drosophila brain does not necessarily correlate with the distribution of serotonergic or dopaminergic neurons. Genetic and pharmacological tools that alter fly brain amine content and TG expression seem to affect H3Q5Aminyl levels. Moreover, TG mutants exhibit alterations in complex behaviors and reduced lifespan compared to wild-type flies. Lastly, docking studies and molecular dynamics simulations support that H3Q5Dop reduces the interaction between DNA and the N-terminal tail of H3, suggesting a possible mechanism by which this PTM alters gene expression.

Our data support that the TG-mediated H3Q5Aminyl contribute to Drosophila brain function.

Financing: Fondecyt 1231556

Stress memory in brain fitness: parental environmental experience shapes offspring susceptibility to neurodegeneration

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Environmental exposure including modern lifestyle habits describes a wide spectrum of risk factors for human health including carcinogenesis. Glioblastoma is the most common, aggressive, and lethal type of glioma. It is highly proliferative and invasive, infiltrates surrounding the brain parenchyma and it is resistant to current treatments. Patients have a heterogeneity in life expectancy even with similar genetic mutations, from weeks to years. Risk factors such as ionizing radiation, allergies, or atopic diseases have been related to a risk for glioma outcomes. Here, we provide a new perspective on the interaction between the tumor and the resistance or the sensitivity of the brain environment depending on paternal environmental or lifestyle determinants, coined as the brain fitness hypothesis. Maternal luminic stress exposure increases oxidative stress in F1 brains without detectable detrimental effects on development. However, inheritable stress hallmark sensitizes brain fitness and promotes accelerated tumor growth and life expectancy differences offspring-sex-dependent. RNAseq experiments done in F1 female and male flies upon maternal light stress determined a sex- and stress-specific hallmark in F1 brains that sensitized brain fitness. Under this continuous light-stressing, dOdf3l2, a sperm gene active in the cytoskeleton is downregulated in F1 brains. dOdf3l2 is expressed in glial cells and shows increased expression in brain samples of tumoral flies suggesting a role in tumor invasion, proliferation, and tumor neurodegeneration. ncRNAs emerge as potential vectors for the transmission and might explain the complexity of inheritable traits and phenotypes acquired as a pleiotropic effect.

Financing: Fondecyt 1210586

Mutations in trpγ the homologue of TRPC6 autism candidate gene, causes autism-like behavioral deficits in Drosophila

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Autism Spectrum Disorder (ASD) is characterized by impaired social communication, restricted interests, and repetitive and stereotyped behaviors. The TRPC6 (transient receptor potential channel 6) represents an ASD candidate gene under an oligogenic/multifactorial model based on the initial description and cellular characterization of an individual with ASD bearing a de novo heterozygous mutation disrupting TRPC6, together with the enrichment of disruptive TRPC6 variants in ASD cases as compared to controls. In order to understand the consequences of mutations in TRPC6 on nervous system function, we used the fruit fly, Drosophila melanogaster, to show that null mutations in transient receptor gamma (trpγ; the fly gene most similar to TRPC6), cause several behavioral defects that mirror features seen in ASD patients, including deficits in social interactions, impaired sleep homeostasis, hyperactivity in both young and old flies, and defects in learning and memory. Some defects, most notably in sleep, differed in severity between males and females and became normal with age. Interestingly, hyperforin, a TRPC6 agonist and the primary active component of the St. John's wort antidepressant attenuated many of the deficits expressed by trpγ mutant flies. Our results provide further evidence that the TRPC6 gene is a risk factor for ASD. In addition, they show that the behavioral defects caused by mutations in TRPC6 can be modeled in Drosophila, thereby establishing a paradigm to examine the impact of mutations in other candidate genes.

Financing: Fondecyt Iniciación 11190601 ANID, Centro CIDI CIICOM Facultad de Odontología Universidad de Valparaíso

Brain and synaptic metabolism in vivo, the power of Drosophila

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The nervous system is known to have a high energy cost when compared to other tissues of the organism, such as the heart and somatic muscle. The knowledge we have of the cellular components that contribute most significantly to energy expenditure suggests that the synapse is proportionally the most expensive. When we consider that there are at least 1000 times more synapses than neurons in the central nervous system, it is clear that we must focus on the synapse to understand the impact of energy management. The pre and postsynaptic compartments of the synapse require ATP-dependent ionic transport mechanisms to maintain the ionic gradients, particularly calcium and sodium. Furthermore, we must consider that ATP requirements may be multiplied many times during neuronal activity, potentially causing limitations unless mechanisms such as increased glucose and oxygen supplies are put in place. Access to the vascular system, which provides these essential molecules, as well as the barriers that they must cross to reach the synapse, is one of the limitations in all nervous systems. The astrocytes that surround synaptic terminals and are required for proper synaptic function are among these barriers. I will present data from my lab that shows the importance of the glia that surrounds synaptic terminals for the energy requirements in the synapse during high frequency activity, with lactate transfer to neurons playing a key role. A comparison of vertebrate and invertebrate brains will also lay the groundwork for a discussion of nervous system requirements independent of their organization.Financing: Fondecyt 1210586, 11200477

SYMPOSIUM 6

Neuronal Circuits and Behavior

Chair: Alexia Núñez and Jorge Mpodozis

Large-scale and local prefrontal neural dynamics during spatial learning

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During spatial learning, subjects progressively optimize their route to the goal, operation supported by the medial prefrontal cortex (mPFC). To this aim, the mPFC integrate, according to current task requirements, relevant information represented in distributed neural networks. However, the prefrontal large-scale activity patterns related to path optimization are poorly known. To assess this issue, we recorded local-field potential and extracellular neuronal firing simultaneously from the mPFC and two relevant structures required for spatial learning, the hippocampus (HPC) and the posterior parietal cortex (PPC) in mice subjected to spatial memory acquisition in the Barnes maze. We found that, during spatial learning, animals executed two behavioral stages: goal-searching and maze-exploration. During the first stage, mice progressively transited from less efficient (non-spatial) to more efficient (spatial) goal-searching strategies. Across learning, the mPFC coordinated with the HPC and PPC at 4 Hz and theta (6-12 Hz) frequency bands. Importantly, both 4 Hz and theta synchronization was higher in the goal-searching stage during the execution of spatial strategies. Hippocampal and parietal 4 Hz and theta oscillations modulated the timing of prefrontal gamma (60-120 Hz) oscillations, modulation that increased during the goal-searching stage when mice implemented spatial strategies. Neurons from the three recorded areas increased their goal-finding selectivity firing index during spatial goal-searching strategy. Interestingly, 4 Hz and theta from HPC and PPC modulated the spike-timing of prefrontal neurons, which was maximum during the goal-searching stage when mice implemented spatial strategies. Thus, dynamics of 4 Hz and theta oscillations allows prefrontal large-scale coordination during spatial learning.

Financing: ANILLO ACT210053 from ANID, Chile; Fondecyt for Initiation into Research Grant (11160251; to IN-O) from ANID, Chile; INICI-UV, Universidad de Valparaíso, Chile.

Role of stress resilience on social behavior and coping styles

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Resilience refers to the ability to quickly adapt to adversity. There are two behaviors that play a fundamental role in stress resilience: social behavior and coping. The first goal was to determine the neuronal activity in two brain areas that play a key role in social behavior: the nucleus accumbens (NAc) and basolateral amygdala (BLA). A microelectrode array was implanted in the NAc and the local field potential (LFP) activity was acquired using a wireless recording system. We found that the high-gamma band power in the NAc was higher only during social approach. Interestingly, rats that were resilient to stress retained this electrophysiological biomarker whereas rats that were vulnerable to stress significantly decreased the high gamma power in the NAc. These results suggest that high gamma activity would be involved in the ability of the NAc to modulate stress resilience and social behavior. In addition, we found that 4-6 Hz frequency band power increased in BLA when rats recalled a fear memory. After, we evaluated whether the experience of social stress is consolidated as a fear memory. Time spent in freezing behavior increased in both social defeat stress and social interaction task. These results suggest that the experience of social defeat is consolidated as a fear memory that generalizes to social behavior. The second goal was to evaluate if coping strategy determines the impact of stress on the brain during aging. Our results suggest that stress-induced passive coping strategy was correlated with impaired working memory and hippocampal neuroinflammation.

Financing: This work has been funded by Interuniversity Center for Healthy Aging, Code RED211993.

Acknowledgments: This work has been funded by Interuniversity Center for Healthy Aging, Code RED211993.

The ventral nucleus of the lateral geniculate: a key neural node for gaze orientation

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The ventral nucleus of the lateral geniculate (GLv) is a prominent retino recipient structure situated in the ventrolateral diencephalon, highly conserved among vertebrates. In birds, it is composed of two main layers: an internal one (GLv-int), that contains tightly packed somas of the projection cells, and an external one (GLv-ex), that contains the main dendrites of the projection cells as well as afferent axonal terminals from different sources. The optic tectum is the main non-retinal source of the GLv afferents, which originate from a characteristic population of cholinergic cells. Other significant afferents originate from the visual hiperpallium (wulst in birds and primary visual cortex in mammals), and several tegmental areas. Retinal and tectal inputs are highly topographic and end homotopically forming concurrent restricted synaptic loci inside the neuropile of the GLv-ex. GLv-int cells are GABAergic, and its efferents follows a descending course through the pretectum, prerubral field and motor tegmentum, to finally target pre-cerebellar pontine nuclei. Despite its prominence and conservative character, the role of GLv in visual operations remains at present unknown. Considering its close link with visual and motor centers, we hypothesized that the GLv may have a role in the generation of visually driven orientation gaze movements. In the present work, by means of field and single unit recordings and local stimulation of restricted GLv loci, we establish for the first time in vertebrates that the GLv is indeed a key node in the generation of visually oriented gaze shifts, involving concerted ego/centric eye and head movements.

Financing: Fondecyt 1210069

Neural rhythms of the motor circuits, are they good or bad?

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At the macro- and mesoscale, brain activity presents distinctive rhythms or oscillations corresponding to the partial synchronization of neuronal populations. These oscillations occur in specific frequency ranges associated with specific behavioral states. The use of deep brain stimulation of subcortical structures in Parkinson's patients has made it possible to record the oscillation of local field potentials in areas such as the subthalamic nucleus and globus pallidus. The presence of strong oscillations in the 11-30 Hz frequency range, termed beta oscillations, led to the notion that these oscillations could be the mechanism underlying the motor symptoms of Parkinson's, as well as to the proposal of their use as a neurophysiological biomarker of motor symptom severity. However, subsequent evidence has narrowed the scope of this notion, suggesting that beta oscillations are part of the physiology of the motor system, and rather reflect the resting non-moving state. In parallel, the simultaneous recording of brain activity in different areas has expanded the concept of oscillations from the local (a single structure), to the global, where multiple structures synchronize or coordinate in a particular frequency range. This characteristic, known as functional connectivity, seems to have a more precise correlation with pathological states and could become, with the appropriate technological feasibility, a highly accurate neurophysiological biomarker.

Financing: CS2018 -7935, CONICYT-PCI Concurso de apoyo a la Cooperación en Investigación Chile – Suecia

SYMPOSIUM

Young Neuroscientist

Chair: Tomás Ossandón

Mitochondrial function during Xenopus laevis spinal cord regeneration

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Spinal cord injury (SCI) is a permanent affliction that affects the central nervous system motor and sensory nerves, resulting in paralysis beneath the injury site. It is estimated that SCI affects between 250.000 – 500.000 new cases worldwide every year. There is an absence of therapies allowing functional recovery, and humans and mammals in general, present limited regenerative capacity. Nevertheless, some non-mammalian organisms can regenerate. Xenopus laevis can regenerate in larvae stages, a capacity that is lost after metamorphosis, allowing the study of the cellular and molecular mechanisms underlying the successful regenerative processes of regenerative stages and comparing them to the non-regenerative ones.

Interestingly, mitochondria have extensively appeared in seminal works playing a pivotal role during SCI events: i) mitochondrial dysfunction is the common event prior to neuronal and glial death; ii) mitochondrial metabolism regulates immune response; iii) mitochondrial number and localization correlates with axonal regenerative capacity and iv) mitochondrial abundance and metabolism regulate neural stem progenitor cells proliferation, and differentiation. This evidence suggests that a more in-depth study of mitochondrial function and regulation is needed to identify potential targets for SCI therapeutic intervention. We studied mitochondrial morphology, dynamics, and function in Xenopus regenerative stages by using electron microscopy, confocal microscopy, RT-qPCR, western blot, and enzymatic function. We determined that SCI resulted in a decreased number and increased mitochondrial area, accompanied by a change in mitochondrial morphology, prevailing a swollen phenotype, which correlates with a decrease in the mitochondrial membrane potential and an increase in glycolytic transcripts and enzymatic activity.

Financing: Funded by Fondecyt 11220624

Acknowledgments: To the students who helped me to obtain these results: Domínguez-Romero ME, Cordero-Véliz C, Hernández C, Villarreal M. My mentors and collaborators: Eisner V, Larraín J

GABAergic modulation in the formation of declarative and recognition memories

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Benzodiazepines are commonly used drugs to treat anxiety in witnesses of crimes. These increase GABA inhibitory effects, which impair the encoding and consolidation of aversive memories. Eyewitness memory is essential in justice. However, memory is malleable leading to false memories that can end in the selection of an innocent in a lineup. Here, we studied whether a low dose of Clonazepam impairs memory encoding as well as consolidation of memory faces and narrative of the event.

We performed two experiments using a double-blind design. Day 1: subjects watched a crime video and received Clonazepam 0.25 mg (CLZ group) or placebo (PLC group) before (Exp. 1) or after the video (Exp. 2) to assess the effect on encoding and consolidation. One week later, the memory was assessed using a present and absent culprit lineup and asking for a free recall.

Regarding encoding, we found that the CLZ group recalled significantly less details on day 2, while central details did not differ between groups. No differences were found for recognition. Regarding consolidation, in the absent lineup, we observed a trend indicating that Clonazepam negatively impacted on correct rejections, leading to more innocents being chosen.

These suggest that a low dose of Benzodiazepine modulates memory encoding and consolidation impacting on the statement and the lineup selection. More studies should be performed with higher doses of CLZ similar to those administered in real life. These results are relevant in the judicial field to assess the reliability of the eyewitness elections.

Financing: Subsidio PICT-2020-SERIEA-02666

High-order functional connectivity: A data-driven approach for studying drug-induced states of consciousness using fMRI

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Understanding neurophysiological underpinnings of different states of consciousness represents a significant challenge in neuroscience, with potential impact on our comprehension of the brain-consciousness relationship and in clinical applications. In this work we leverage recent developments in information theory to capture the high-orderinteractions between brain regions that best characterize states of consciousness induced by mind-altering drugs. Resting state fMRI data from individuals under the influence of LSD, psilocybin, MDMA, and ketamine were analyzed. High-order functional connectivity (HOFC) was employed to measure high-order interactions between brain regions. Its potential to discriminate between drugs was validated using machine learning.HOFC revealed distinct connectivity patterns for each drug. Serotonergic drugs (LSD,psilocybin) were dominated by reduced HOFC, while ketamine by the opposite. All drugs induced hypoconnectivity in frontal regions. We obtained an almost perfect drug classification accuracy using HOFC features. Our work provides a unique, accurate and parsimonious description of brain activity associated with different states of consciousness induced by mind-altering drugs. In general, these states could be characterized by reconfiguring fronto-temporal connectivity, hyperconnectivity between multimodal and subcortical regions and hypoconnectivity between sensory and integrative regions, as previously described by the current neuroscientific literature of psychedelics. Further investigations with diverse drugs, recording methods, and larger sample sizes are imperative to elucidate the ability of HOFC to discriminate between healthy, non healthy and non-ordinary states of consciousness, and to pave the way towards clinical applications.

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The role of astrocytes and its gliotransmitter release by connexin 43 hemichannels in depression.

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Our previous studies have shown that depression, based on the chronic restraint stress rodent model, is caused by increased release of astroglial glutamate, ATP and D/L serine mediated by astroglial Cx43 hemichannels in the ventral hippocampus, leading to increased extracellular glutamate, ATP and an overactivation of post-synaptic NMDA receptors (NMDARs), suggesting that depression can be prevented and treated by targeting astrocytes. However, when we attempted to understand the role of glucocorticoids in this process, unexpectedly, we found that depressive-like symptoms appear together with an increase in astroglial gliotransmitter release only after plasmatic and hippocampal corticosterone decrease, which occurs 24 hours after the end of stress, rather than when glucocorticoids are high during stress. In fact, decreasing corticosterone synthesis induces depressive-like symptoms, while maintaining corticosterone levels in plasma or intra-hippocampally prevents depressive-like symptoms from developing. Our results show that depression is the result of the decrease in glucocorticoids post-chronic stress, and that glucocorticoids decrease astroglial gliotransmission in the ventral hippocampus, which is increased once glucocorticoid levels are reduced. These results may suggest that reducing stress slowly rather than quickly, may be a way to prevent the development of depression.

ORAL COMMUNICATIONS I

Evolution of developmental systems that shaped the neocortical connectome

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Neural connections of the cerebral cortex are fundamental for everyday sensory-motor and higher-order functions. Although only mammals evolved a 6-layered cerebral cortex (or neocortex), key evolutionary innovations that made our brains unique include the origin of the corpus callosum in eutherian ancestors, and expansion of neuronal numbers by abventricular neurogenesis in primates. How these major events originated remains, however, unknown. Here, I will present recent and unpublished data of how subtle changes in brain development might lead to major evolutionary innovations of neocortical circuits. For example, connections between cortical areas (i.e. the connectome) follow a template that likely evolved before callosal origin, and callosal formation requires a unique remodeling of the cortico-septal midline. By exploiting in-pouch development of marsupials, we identify conserved patterns of spontaneous cortical activity revealed by GCaMP6s and two-photon live imaging, suggesting new morphogenic roles of electrical activity in shaping cortical circuits. Our ability to manipulate genetic and electrical activity in live neuronal circuits demonstrate that lineage-specific patterns can be elicited by subtle alterations of embryonic events, highlighting the role of developmental systems drift on the origin of complex traits.

Evolution and development of the binocular vision in mammals

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The way an animal orient and conjugate its eyes is crucial in determining how it will enact a visual picture of its surrounding world. Comparative studies have stablished that the visual field configuration strongly correlates with visual ecology and behavior. For instance, highly convergent eyes and orbits provide wide binocularity to hunting, nocturnal species, whereas lateralized eyes and orbits provide a panoramic view to preyed species. Eye position also influences the development of high-acuity retinal areas, the degree of ipsilateral retinal projections, and the ocular dominance and orientation selectivity at cortical levels. However, how proper eye orientation is attained during development remains unexplored. Here, we show that the eyes and orbits of Octodon degus develops and converge postnatally to expand the binocular field from ~20° at P5 to ~60° in adults. In parallel, the high-acuity area centralis and visual streak develop from a postnatally homogenous retinal cell distribution. Additionally, escaping in response to aversive stimuli in the upper binocular field matures in parallel with the binocular expansion and retinal specializations. Our results are the first detailed description of how postnatal changes in eye and orbit orientation both configure the binocular visual field and correlate with changes in retinal topography and behavior, providing new basis to understand the mechanisms driving the binocular vision diversity in mammalian evolution.

Financing: Proyecto FONDECYT Postdoctorado N°3220871

How has the timing of neurodevelopment shaped the connectivity of the mammalian brain?

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There is remarkable variation among mammalian brains, particularly the neocortex, which vastly expanded in humans and is responsible for many aspects of higher order cognition. Whereas the majority of studies comparing the mammalian neocortex have examined species within the placental (eutherian) lineage, there are also intriguing evolutionary divergences between placentals and marsupial mammals. For instance, while the two neocortical hemispheres of marsupial mammals are interconnected via the anterior commissure, placental mammals evolved a novel dorsal commissural route: the corpus callosum. To identify candidate differences that may underlie the emergence of the corpus callosum, we used birthdating, in pouch and in utero electroporation and single-cell RNAseq to investigate the endogenous developmental time course of representative species from these two lineages: the mouse and the Australian marsupial fat-tailed dunnart. We found that developmental subprocesses do not temporally scale in a uniform manner, and identified the lack of a progenitor cell subtype in marsupials as a candidate factor that may contribute to this distinct developmental timing. We then transfected genetic tools in the cortex of both species to manipulate developmental timing, and found that speeding up neuronal maturation in a mouse caused ectopic connectivity through the anterior commissure, whereas slowing down neuronal maturation in a dunnart resulted in an ectopic corpus callosum-like structure at the dorsal midline. This work provides clues about the evolutionary mechanisms that drive the emergence of the corpus callosum as a complex trait in placental mammals, and experimentally demonstrates the importance of developmental timing in shaping mammalian brain structures.

Vagal nerve stimulation in Multiple Sclerosis: a non-pharmacological approach to reduce neuroinflammation and disease progression

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Multiple Sclerosis (MS) is a neurodegenerative disease originated in the loss of myelin (a specialized oligodendrocytes (OL)-derived membrane) at the central nervous system (CNS). Demyelinated areas (i.e. lesions) contain an inflammatory environment due to reactive astrocytes and proinflammatory microglia activity. This environment impairs the spontaneous regeneration of myelin aggravating the symptoms of MS patients. A promising treatment for reducing central and peripheral inflammatory conditions is the electrical stimulation of the vagus nerve (VNS). Recent research indicates that VNS reduces proinflammatory cytokine levels, microglia, and macrophages infiltration; however, the effect of VNS on neuroinflammation and progression of MS has not been determined. To study this we have implemented an pre-clinical model of MS by injecting lysolecithin (LPC, a toxin that kills OLs specifically) in CNS white matter tracts of C57BL/6 mice (P45-70). After 7 days post LPC-injection, by implanting a stimulating electrode, mice were treated with VNS in vivo. Importantly, treated mice showed a reduction in the population of reactive astrocytes along with a change of microglia from a proinflammatory to an anti-inflammatory phenotype compared to control untreated (sham) animals. In the same line, increased levels of the anti-inflammatory cytokine TGFβ-1 were detected in VNS-treated mice. Notably, more myelinated area was founded in the VNS group, along with an improved locomotor, cardiovascular and bladder function in treated mice. Our results suggest that VNS revert the MS progression signs, improving remyelination by modulation of proinflammatory environment of lesions.

Financing: Funded by FONDECYT 1210940 to FO

Acknowledgments: Special thanks to Dr. Del Rio's lab (PUC), Dr. Amador's lab (USS) and to Ignacio Silva and Dr. Varas from Myelin lab

Serotonin modulates spatial working memory in Drosophila melanogaster

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Serotonergic projections in the CNS of vertebrates promote changes in the structure and activity of brain areas relevant to cognitive flexibility associated with spatial learning and memory. In Drosophila, spatial memory, which is necessary to guide navigation, requires subpopulations of ring neurons of the ellipsoid body (EB). Several studies support that the EB is innervated by a subpopulation of serotonergic neurons named ExR3 neurons, which belong to the PMPD cluster and can modulate the activity of ring neurons. Here, we have developed a spatial conditioning paradigm to measure spatial working memory in flies. Our task consisted of a single training protocol that lasts 3 minutes and is successful at generating a short-term spatial memory that is detected 30 minutes after training but disappears 2 hours later. Also, we tested whether the disruption of the serotonergic system affects the spatial working memory. We found that dSERT mutant flies, which exhibit reduced activity of dSERT in all serotonergic neurons, form a spatial memory at 2 hours after a single trial. Moreover, we found that silencing or activating ExR3 neurons dramatically impaired short-term spatial memory. Together, our results demonstrate that the activity of serotonergic neurons modulates spatial working memory in Drosophila. We discuss that the ExR3-ring neuron serotonergic pathway is necessary for forming spatial memory.

Financing: Supported by ANID fellowship #21191820, FONDECYT #1231556 and FONDECYT #1210586

Impact of microbial consortia producing neuroprotective metabolites in a model of Parkinson's disease in Drosophila melanogaster

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The human gut microbiome is a rich and complex microbial community that plays critical roles in host health. In recent years, bidirectional communication, described as the microbiome-gut-brain axis, has demonstrated its influence on the nervous system. The synthesis of neurometabolites by gut microbiome bacteria has been found to be significant in nervous system modulation in this communication.

The purpose of this study was to see how microbial consortia tailored for GABA and butyrate synthesis affected neurodegeneration in an animal model. For this, we use genomic scale models and the SteadyCom microbial community design algorithm to create microbial consortia of human gut bacteria optimized for GABA and butyrate production. We characterized and confirmed GABA and butyrate-producing microbial consortia created in silico in a batch bioreactor at the laboratory scale, obtaining growth, bacterial neurometabolite synthesis, substrate consumption, and bacterial abundance during fermentation. We investigated the effect of a selected consortium on neurodegeneration in a Parkinson disease (PD) model in Drosophila melanogaster, where we measured locomotor capacity, survival, and the metabolite profile of the fly heads after seeding the larvae with fly bacteria or the human bacterial consortium.

Our findings reveal that treatment with the human bacterial consortium has no deleterious impact on control D. melanogaster survival, but more critically, it recovers the PD flies' locomotor phenotype at 10 and 25 days of age. Furthermore, PD flies have a different metabolite profile in terms of neurotransmitters, amino acids, and the TCA cycle, which is restored in PD flies implanted with the microbial community.

Tmbim6 inhibits apoptosis of vulnerable neurons in parkinson´s disease

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Background: Parkinson´s disease (PD) is a common neurodegenerative syndrome characterized by dopaminergic neurons death in substantia nigra (SN), and movement disorder. Unfortunately, PD has no cure. TMBIM6 is an anti-apoptotic protein that integrates several cellular processes, and arises as protective factor in other disorders, but its role in PD is unknown. Here, we hypothesize that TMBIM6 plays a neuroprotective role in PD. **Methods:** First, we analyzed TMBIM6 expression in neurons and, in PD postmortem samples by bioinformatic analyses. Then, we used inhibited TMBIM6 in cortical neurons (CXNs) by TMBIM6-antagonist, and apoptosis and mitochondrial homeostasis were evaluated. Also, TMBIM6-antagonist was injected on SN of mouse, and the motor skills and dopaminergic neurons were determined. Finally, we overexpressed TMBIM6 on SN4741 dopaminergic cell exposed to sporadic PD models, and apoptosis were evaluated. **Results:** In brief, we had shown in sillico that TMBIM6 is highly expressed in dopaminergic neurons, and downregulated in PD postmortem samples. Also, inhibition of TMBIM6 causes apoptosis and mitochondrial impairment in CXNs, and on SN causes dopaminergic neuron death and a deficit in locomotor skills. Finally, the overexpression of TMBIM6 decreases apoptosis of dopaminergic cells in PD models. **Discussion:** We observed that TMBIM6 inhibition on SN triggers cell death and decreased motor skills, suggesting that TMBIM6 is critical to survival of adult neurons. Additionally, in an in vitro PD model, TMBIM6 protects cells form both apoptosis and mitochondrial impairment, principal features of PD-like neurodegeneration. Taken together, our work strongly suggests a possible neuroprotective role of TMBIM6 in PD.

Financing: FONDECYT Regular 123082. Acknowledgments: Cell Death and Biomedicine Lab, University MayorDr. Diego Rojas-RiveraDr. Rene VidalDr. Mario Sanhueza

A possible role of mitochondrial permeability transition pore (MPTP) on synaptic failure induced by caspase-3 cleaved tau

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During Alzheimer's (AD), tau protein suffers from abnormal post-translational modifications, including cleaving by caspase-3. These tau forms affect synaptic plasticity contributing to the cognitive decline observed in the early stages of AD. In addition, caspase-3 cleaved tau (TauC3) impairs mitochondrial function and organelles transport, which are both relevant processes for synapse. We recently showed that the absence of tau expression reverts age-associated cognitive and mitochondrial failure by blocking the mitochondrial permeability transition pore (mPTP). mPTP is a mitochondrial complex involved in calcium regulation and apoptosis. Therefore, we studied the effects of caspase-3 cleaved tau (TauC3) against synaptic plasticity alterations including dendritic spine, synaptic vesicle, and cognitive function and the possible role of mPTP. We used mature hippocampal mice neurons to express a reporter protein (GFP, mCherry), coupled to full-length human tau protein (GFP-T4, mCherry-T4), and coupled to human tau protein cleaved at D421 by caspase-3 (GFP-T4C3, mCherry-T4C3) and synaptic elements were evaluated. Treatment with cyclosporine A (CsA), an immunosuppressive drug with inhibitory activity on mPTP, prevented ROS increase and mitochondrial depolarization induced by expression of TauC3 in hippocampal neurons and tau (-/-) mice models. Interestingly, TauC3 significantly reduced dendritic spine density (filopodia type) and synaptic vesicle number in hippocampal neurons. Also, neurons transfected with TauC3 showed a significant accumulation of synaptophysin protein in their soma. More importantly, all these synaptic alterations were prevented by CsA, suggesting an mPTP role in these negative changes derived from TauC3 expression

Financing: ANID, FONDECYT 1200178 (RAQ); Universidad Autónoma de Chile (RAQ, MAO)

ORAL COMMUNICATIONS II

Patients recovered from COVID-19 with anosmia present functional and structural brain alterations

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Coronavirus disease 2019 (COVID-19) is emerging as one of the greatest public health crises of our times. While COVID-19 primarily affects the respiratory system, other organs including the brain can be involved. Increasing evidence indicates that recovered COVID-19 patients present neuropsychiatric alterations and thinning of certain cerebral cortex areas, especially those connected to the primary olfactory cortex. Also, it has been suggested that patients with COVID-19 that have anosmia could present affection of orbitofrontal regions. Given this background it is highly relevant to evaluate the possibility of alterations at the brain level in recovered COVID-19 patients. Here we present preliminary study data analysis.

We include 72 (33 females) recovered COVID-19 patients (mean age 42, range [18:66]; 38 with anosmia during infection; 29 hospitalized because of respiratory symptoms) that were asked to resolve a Reversal Learning Task (RLT) while their brain activity was measured with fMRI

The findings are (1) in those patients that had anosmia there here was a decrease of activity in several prefrontal and subcortical regions and (2) a diminished cortical thickness in the left superior frontal gyrus, regardless of the severity of respiratory symptoms. Our results suggest that anosmia can be used as a marker of brain alterations in patients recovered from COVID-19. It could be important to follow the track of these patients in order to investigate possible long-term consequences of COVID-19 on the nervous system.

Financing: Proyecto de Investigación Clínica Alemana ID 1033;Proyecto interno UDD 2020_102 UDD

Theta activity related to proactive cognitive control negatively correlate with social acceptance in childhood

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Inhibitory control can influence children's social behavior development, peer acceptance, and how others perceive them. Inhibitory control reflects the capacity to regulate a response after assessing the information about an action's consequences (reactive cognitive control) and anticipating challenging situations in the environment (proactive cognitive control). Although frontal theta activity (3-8Hz) reflects cognitive control (CC), the specific role of reactive and proactive CC in the degree of social peer acceptance during childhood is still unclear.

To identify the social network of each peer group, we designed a game in which children must select classmates to distribute and allocate tokens. Thus, a social network was built for each classroom based on the number of individual selections and received tokens. Electroencephalographic (EEG) recordings were made of children performing an inhibitory control task (Go Nogo).

Six hundred and twenty-fives children (8-10 years old) from 6 schools with a neurodiverse educational program participated. Twenty-six social networks were built. Forty-six EEG recordings were performed on children from 3 classrooms. Time-frequency analysis showed i) an increase in theta power (4-6 Hz) in the left-frontal electrodes related to the sequence of Go stimuli (seqGo) as a proxy of proactive CC; and ii) an increase in alpha power (8-15 Hz) in medial frontal electrodes related to Nogo stimuli. Only theta power related to seqGo correlated with peer acceptance (rho= -0.44; p=0.0025, Spearman test). Theta power related to seqGo might reflect free-model learning leading to more spontaneous social interactions and, subsequently, obtaining social acceptance.

Cortical white matter hyperintensities are associated with locus coeruleus atrophy in elder subjects

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White matter hyperintensities (WMH), often observed in the elderly, are commonly interpreted as vascular abnormalities contributing to age-related cognitive decline. It has been hypothesized that an imbalance in norepinephrine (NE) signaling could lead to "hypometabolism" by decreasing astrocyte metabolism, which has been proposed as an important cause leading to local demyelination. We hypothesize that structural atrophy in human Locus Coeruleus (LC) leading to NE deficiencies could contribute to the pathophysiology of WMHs by affecting astrocytic metabolism through astrocytic beta-adrenergic 2 receptors. To test this hypothesis, we here quantitatively analyse WMH and correlate their incidence with LC atrophy in a Chilean elder cohort (N=94) and ADNI cohort (n=200). We found that LC atrophy is related to increased WMHs, mainly in frontal lobes. We found that LC atrophy significantly mediated the relation between WMH and gait speed beyond vascular contributions. Furthermore, we compare the cortical spatial overlap of WMH density with the expression of beta-adrenergic receptor's gene expression related to LC atrophy. Together, our results provide a comprehensive framework of a systems-level mechanism giving rise to WMH in aging.

Financing: FONDECYT POSTDOCTORADO 3230557

Acknowledgments: We thank the subjects who participated in the study.

Deep Learning for the Detection and Explanation of Subcortical Anomalies in Ataxia Telangiectasia: Towards Personalized MedicineDeep learning para la detección y explicación de anomalías subcorticales en Ataxia Telangiectasia: hacia la medicina personalizada

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Ataxia telangiectasia (AT) is a disease characterized by cerebellar neurodegeneration and movement disorders thought to be linked to subcortical structures. Our aim was to detect and explain these anomalies evaluating maps of Apparent Diffusion Coefficient (ADC) derived from Diffusion-Weighted Imaging (DWI) and Cerebral Blood Flow (CBF) perfusion maps based on pseudocontinuous Arterial Spin Labelling (pCASL) in 16 children with AT.

We assessed 7 regions of interest (ROI): caudate, hippocampus, pallidum, putamen, thalamus, cerebellar gray matter (CGM), and cerebellar white matter (CWM). First, we implemented a normative deep autoencoder (using 99 controls) to reconstruct the diffusion and perfusion data. Second, SHAP values were used to identify influential prediction features. Lastly, we correlated reconstruction errors (RE) with clinical patient scores using linear regression. All analyses were corrected by sex, age and cerebral volume.

Data was correctly reconstructed in controls but not in patients, who showed significantly higher RE. SHAP explainability showed that decrease in estimated perfusion values was due to caudate, putamen, hippocampus, CGM, thalamus, and CWM perfusion. The analysis revealed that increase in estimated diffusion values was due to CGM perfusion and diffusion, and CWM diffusion, whereas reduction was due to caudate perfusion.

Clinical analysis showed negative correlation between hyperkinesia and RE of hippocampal and pallidal perfusion, and of diffusion in all ROI (except thalamus). We identified correlations with perfusion RE in ataxia and bradykinesia with caudate (positive), bradykinesia and dystonia with pallidum (inverse), and dystonia with putamen (positive).

Our study suggests considering subcortical areas for AT treatment. Normative autoencoder models could guide personalized interventions.

Acknowledgments: The authors wish to thank the children, adolescents, and families who took part in the data collection for the study. Keywords: cerebellum, subcortical, MRI, movement disorders, ataxia telangiectasia, autoencoder, deep learning, personalized medicine.

Neural mechanisms underlying the domain-general processes in cognitive control in healthy adults and multiple sclerosis patients

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Daily, we perform actions to achieve our objectives. This behavior is linked to cognitive control (CC), which entails the regulation of our actions with flexibility and efficiency. CC relies on coordination between prefrontal cortex and other areas distributed and highly interconnected cortical and subcortical regions.

The study suggests that the Multiple-Demand (MD) network plays a pivotal role, acting as a system that rapidly connects with other brain networks.

In neurological conditions like Multiple Sclerosis (MS), where CC is impaired, changes in brain oscillations in theta band are observed. It is believed that this impacts the coordination of brain networks involved in CC. While measuring CC is complex, it is suggested that different cognitive tasks share a general cognitive processing system utilizing theta synchronization in the MD network.

The study analyzed 19 MS patients and 16 healthy volunteers in working memory and inhibitory control tasks. At the behavioral level, no significant group differences were found. However, at the brain level, MS patients exhibited decreased theta activity when anticipating conflicting stimuli, whereas healthy volunteers showed increased frontal activity. In the working memory task, MS patients displayed reduced theta activity during the maintenance phase, while healthy volunteers exhibited the opposite pattern.

In conclusion, the study highlights brain changes in MS patients during cognitive processes, particularly in the theta frequency. This could signify issues in coordinating key brain circuits for CC. These findings enhance our understanding of cognitive deficits in MS and suggest that brain oscillations could serve as biomarkers for assessing cognitive deficits.

Financing: - Beca Doctorado Nacional ANID - Fondos de investigación del Laboratorio de Neurociencia Social y Neuromodulación, Universidad del Desarrollo.

Enhanced astrocytes activity, excitation/inhibition imbalance and disrupted-temporal integration in the hippocampus of pentylenetetrazole kindlingmodel of epilepsy.

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Epilepsy is a neurological disorder marked by neural circuit hyperexcitability and hypersynchrony. It's linked to increased glutamatergic and reduced GABAergic neurotransmission. However, the impact on excitation-inhibition (E/I) balance and key hippocampal circuitry, including neurons and astrocytes, remains unclear. We studied E/I balance in the pentylenetetrazol (PTZ)-induced chronic epilepsy model. Using electrophysiology, we recorded simultaneous glutamatergic and GABAergic neurotransmission in hippocampal CA1 pyramidal neurons of kindled mice. We assessed excitatory and inhibitory evoked postsynaptic currents at -40 mV (EPSCs/IPSCs), calculating E/I ratios, paired-pulse ratios (PPR), and spontaneous activity (sPSCs).To explore E/I imbalance effects, we evaluated the temporal integration of CA1 neurons, stimulating different pathways in PTZ and control animals with astrocytes activated by PAR1 agonist TFFLR. PTZ-kindled mice had a twofold E/I amplitude increase vs. Controls, lower PPR in EPSCs, and this normalized through astrocyte metabolic inhibition. PTZ mice had higher postsynaptic currents frequency (sEPSCs) and increased input/output function with PTX, contrasting lower spike threshold. An elongated integration window emerged in CA1 neurons, seen when astrocytes were overactivated in controls. In summary, the PTZ-kindled group exhibited elevated glutamate release due to heightened glioliberation. Chronic PTZ-induced epilepsy results in E/I dysregulation, contributing to CA1 neuron integration dysfunction.

Financing: This research was funded by Universidad de Valparaíso DIUV-CI Grant N°01/2006 (C.B.). Partial support was received from the Chilean National Agency of Research and Development (ANID) through FONDECYT Grant N°120-0474 to RS-Z. and C.B. F.A. is recipient of fellowship "Beca de Magíster en Ciencias Biológicas mención Neurociencias"

Acknowledgments: To Dr. Christian Bonansco. He had over 20 years of research dedicated to the neurobiological basis of epilepsy and the astrocyte's role in regulating synaptic function in the hippocampus

B1 receptors modulate feedforward and feedback inhibition at rod bipolar cell terminals and contribute to shape scotopic visual response in rat retina

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Type 1 cannabinoid receptors (CB1Rs) are expressed in major retinal neurons within the rod-pathway suggesting that they modulate the scotopic retinal network. However, how exactly do CB1Rs modulate night visual processing

remains poorly understood. Here, we report that in rat inner retina, activation of CB1Rs reduce glutamatergic feedforward signaling at rod bipolar cell (RBC) terminals and eliminate reciprocal GABAergic feedback inhibition back onto RBC terminals mediated by A17 amacrine cells. Activation of CB1R, however, does not modify lateral GABAergic feedback inhibition onto RBC terminals mediated by other types of amacrine cells. Notably, CB1R-mediated reduction of feedforward signaling at RBC terminals is independent of modulation of voltage gated Ca^{2+} channels or PKA signaling, but requires G-protein alpha subunit, cAMP and EPAC1/2 signaling. We also found that by modulating RBC dyad synapse, CB1R contribute to sharpen the time course of visual response as its activation prolongs, whereas its inhibition accelerates dim light rod-driven visual signals in vivo. Altogether, these results suggest that by regulating feedforward and feedback inhibition at RBC dyad synapse, CB1Rs contribute to shape scotopic visual response, highlighting a role for cannabinoid signaling in the fine-tuning dim light vision in the inner mammalian retina.

Financing: This work was supported by the Chilean government through FONDECYT Regular # 1201848 (AEC). S.F.E was supported by a PhD fellowship from ANID 21191436

Cortical-bulbar feedback supports behavioral flexibility during rule reversal.

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Mice flexibly adjust their behavior to environmental changes and excel at recognizing odorants in complex sensory conditions; however, little we know about: (1)how changes in stimulus contingency modify odorant representations and (2)how changes in odorant representations causally relate to behavioral adjustments. The piriform cortex(PCx) receives sensorial input from the olfactory bulb(OB), and input from associative areas(e.g., orbitofrontal cortex) and sends dense feedback that selectively modulates one of the OB output channels(mitral cells). Therefore, PCx is ideally positioned to integrate sensorial input and behavioral contingencies to modulate OB output in tune with behavioral goals. To study the role of cortical-bulbar feedback(CBF) in supporting flexible behaviors, we trained mice in a Go/No-Go task with rule reversal guided by odor and sound cues. Within the same session, reward contingencies were reversed across blocks of contiguous trials, rewarding either cue type depending on the block rule and the animal decision(report lick). We monitored CBF activity(GCaMP) in mice engaged in the task using multiphoton microscopy. CBF boutons exhibited dense and diverse responses that change mirroring the task block structure. The response changes observed after each rule reversal slightly lagged in updating in correlation with the behavioral switch. Classifiers trained to decode behavioral contingency rapidly increased their performance after cue delivery and before the animal's decision. Optogenetic suppression experiments(Jaws) suggest that mice rely on CBF to adapt their behavior after each rule reversal. Our results indicate that CBF multiplexes information about stimulus identity and contingency that is rapidly re-formatted according to changes in the reward contingencies.

Financing: NIH: 5R01DC014487NSF: 1656830EEA Grants: RO-NO-2019-0504

POSTER SESSION I

Presynaptic distribution of G-protein receptors kinases on nucleus accumbens synaptosomes from rats

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Dopamine (DA) is a neurotransmitter that regulates movement and motivation. A dysregulation of DA transmission has been found in disorders like drug addiction. In this sense, a low expression of dopamine D2 receptors (D2R) in the nucleus accumbens (NAc) was found in rats with a high susceptibility to develop psychostimulants self-administration. Then, which mechanism accounts for this differential expression of D2R in rats? G-protein receptors kinase (GRKs) are enzymes that regulate G-protein receptors desensitization and internalization. Data in KO mice have shown that GRK2, GRK3 and GRK6 regulate the dopaminergic system and the locomotor effects of drugs of abuse, potentially through D2R. However, is unclear whether GRKs regulation of D2R is occurring in the presynaptic or postsynaptic sites in the NAc. We aim to give evidence on this subject by determining the presynaptic expression of GRK2, GRK3 and GRK6 in NAc synaptosomes from rats. Brains from adult Sprague Dawley rats were obtained and the NAc dissected. Synaptosomes were obtained using a discontinuous Percoll gradient. Then, NAc synaptosomes were seeded in coverslip and immunofluorescence for tyrosine hydroxylase (TH) plus GRK2, GRK3 or GRK6 was performed. Our preliminary data show a high colocalization of GRK2 in TH positive synaptosomes. On the other hand, we found a low colocalization of GRK3 and GRK6 on TH positive synaptosomes. These results suggest that only GRK2 is expressed in dopaminergic terminals in the NAc. Our following experiments will aim to reveal the effect of presynaptic and postsynaptic GRKs on D2R trafficking in cell lines.

Financing: Funded by Fondecyt Postdoctorado 3230573

Structural comparison of the pallial eyes in two pectinid species endemic to Chile

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The visual system of the Pectinidae family (bivalve molluscs) has aroused the interest of a large number of studies, mainly because of the complexity of their eyes due to multiple morphological and functional adaptations to their habitat. The non-cephalic eyes of the scallops are composed of a cornea, lens, pigmentary epithelium, a double inverted retina and a concave mirror. Previous studies have described the retina, lens and mirror of the scallop eye, however, there are still cellular components that have not been explored creating a gap in the complete understanding of how the eye works in these animals, and in what way the ultrastructural components can give an explanation to the results found in functional and optical studies. The peruvian scallop Argopecten purpuratus and the patagonian scallop Chlamys patagonica are two important hydrobiological resources which inhabit two different latitudes in Chile. Using optical and transmission electron microscopy, with thin (20 µm) and ultra thin sections (90 nm), we compare and characterize the components of the pallial eyes of these two species. Ultraestructural analysis of the eyes of these animals shows that the cellular components are conserved between species, however the size of the different cell types varies interspecifically. In addition, the presence of actin was detected in multiple cell types inside the eye, this would explain the ability to stretch or contract detected in some cells. These structural adaptations reaffirm the refined morphology and the importance of vision for this bivalve family, despite having a limited system for neuronal processing.

Lysine Specific Demethylase 1 (LSD1): epigenetic and neurochemical transmission talking during compulsive behavior development.

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Compulsive behavior (CB) corresponds to the inability to halt an ongoing action and is a symptom of drug addiction and obsessive-compulsive disorder (OCD). Dopaminergic alterations in the mesolimbic system have been identified in CBs, although the molecular mechanisms explaining their development and persistence are still unknown. The perpetuation of behaviors is related to epigenetic changes that modulate the expression of genes involved in the strengthening of synapses. LSD1 is an epigenetic enzyme that represses or activates transcription depending on the histone substrate modified. neuroLSD1, a neuro-specific splicing variant, regulates neurite growth and morphogenesis during development and neuronal excitability in adults, functioning as a dominant-negative epigenetic molecular device of the ubiquitous variant. The proportion of LSD1 variants is dynamic facing different environmental conditions. Our results show that an acute amphetamine (AMPH) injection increases total LSD1 protein levels in the striatum of mice but decreases after its repeated administration. Conversely, neuroLSD1 null mice do not show differences in LSD1 levels after repeated doses of AMPH, in addition to exhibiting a decreased electrically evoked dopamine release in the Nucleus Accumbens in response to AMPH. One well-validated animal model of OCD is that induced by the repeated administration of Quinpirole, a D2/D3 receptor agonist. Results obtained with this OCD model show a significant increase in LSD1 protein levels in the striatum compared to those treated with Saline and AMPH. We suggest that LSD1 participates in the establishment of an epigenetic program that allows the development of CBs.

Financing: Beca de Doctorado Nacional 21221349, Agencia Nacional de Investigación y Desarrollo (ANID). Proyecto Puente UC, to María Estela Andrés.

Early life Ethanol-exposure alters splicing machinery in rat brains

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Prenatal ethanol exposure is associated with neurodevelopmental defects and long-lasting cognitive deficits, grouped as fetal alcohol spectrum disorders (FASD). A hallmark of FASD is memory and learning deficit linked to diminished synaptic plasticity in the hippocampus. The molecular mechanisms underlying FASD are incompletely characterized. Alternative splicing modulation is crucial for neurodevelopment and synaptic plasticity. Here we explore the effects of early-life ethanol exposure over alternative splicing modulation. FASD model in rats demonstrates that splicing factors expression is differentially altered by ethanol in a time and brain nuclei-dependent way. This is also correlated with alternative micro-exons incorporation into the transcript of target genes. Together these data highlight alternative splicing modifications as a possible mechanism of ethanol-induced brain alteration in FASD.

Financing: PEW Biomed Innovation-2021-A-18047 to PH; PUENTE-2023-2 to EA; and postdoctorado ANID n°3230704 to MO.

Postsynaptic distribution of GRK2 and GRK3 in the nucleus accumbens and ventral tegmental area of rats

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Motivated behaviors like drug addiction are influenced by the neurotransmitter dopamine (DA). Its binding to dopamine G protein-couple receptors (GPCR) mediates dopamine signaling. Precise control of GPCR-mediated signaling pathways is crucial for appropriate cellular responses. G protein-couple kinases (GRK) constitute an enzyme group that orchestrates desensitization, internalization, and recycling processes of GPCRs. The dopamine D2 receptor (D2R) influences susceptibility to drug addiction. Using KO mice for each GRK, it has been demonstrated that GRK2 and GRK3 regulate the dopaminergic system, possibly via D2R. Regulation of localization of D2R by GRKs in presynaptic or postsynaptic sites of the nucleus accumbens (NAc) and ventral tegmental area (VTA) remains undetermined. The aim of this study is to determine the postsynaptic levels and location of GRK2 and GRK3 in NAc and VTA of rats. Brains from adult Sprague Dawley rats were perfused with 2% paraformaldehyde. Then, serial sections of NAc and VTA were obtained, and immunofluorescence assays for GRK2 and GRK3 plus DARPP32 or tyrosine hydroxylase (TH) were performed. We found that colocalization of GRK2 and GRK3 with DARPP32 in the NAc was partial and high, respectively. On the other hand, colocalization of GRK2 and GRK3 with TH in the VTA was high and partial, respectively. Our preliminary conclusion is that GRK2 has a high postsynaptic colocalization with dopaminergic neurons in the VTA, while GRK3 is mainly found in striatal neurons in the NAc. Our upcoming experiments will seek to reveal the effect of presynaptic and postsynaptic GRKs on D2R trafficking in cell lines.

Financing: Funded by Fondecyt Postdoctorado 3230573

Reelin involvement in hypothalamic autophagy

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Autophagy is a conserved degradative process essential for the maintenance of homeostasis. Cytoplasmatic material and dysfunctional organelles are sequestered in autophagosomes which fuse with lysosomes to be degraded. Autophagy is particularly relevant in neurons, as post-mitotic cells. The biogenesis and transport of autophagosomes to fuse with lysosomes is a dynamic process called autophagic flux. Defects in neuronal autophagy, i.e., initiation or flux events, are associated with several pathologies. The hypothalamus is a brain region critical to body metabolism; a high-fat diet (HFD) inhibits hypothalamic autophagy contributing to obesity, a risk factor for multiple neurological disorders. Reelin is a multifunctional secreted glycoprotein in the brain that binds to ApoER2. Obese mice have reduced reelin levels and cognitive impairment due to neuronal loss. Reelin administration regulates feeding behavior, body weight and modulates POMC neurons activity, part of the neuronal circuit responsible for controlling feeding behaviors. We evaluate how reelin impacts autophagy in the hypothalamic cell line N43/5 treated with Palmitic Acid (PA) as an in vitro HFD. We detect the presence of the reelin receptor and the pathway's activation. Then, we determine the effect of reelin on autophagy, finding an increase in autophagosome formation (increased LC3 positive structures). PA treatment decreases autophagic flux and alters endo-lysosomal compartments, affecting POMC neurons' function. Pre-treatment with reelin maintains autophagic flux in the presence of PA. Here, we show for the first time the role of reelin in maintaining basal autophagy and its neuroprotective effect against impaired degradative processes caused by HFD in the hypothalamus.

Financing: Funded by FONDECYT Regular 1200393 - MPM and Beca Doctorado Nacional ANID 21190369 - CAG.

Modulation of the subcellular distribution of TRPM8 channels by S29 phosphorylation

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TRPM8 ion channel is a critical component of the molecular machinery responsible for detecting cold temperatures in the somatosensory system. This polymodal thermo-TRP channel is activated by cold, cooling compounds such as menthol, voltage, and osmolality rises. Modulation of the TRPM8 function involves several forms of regulation, including phosphorylation. In that regard, we previously identified that serine 29 phosphorylation downregulates TRPM8 function, decreasing cold- and menthol-evoked responses and reducing the number of active channels at the plasma membrane.

To further understand how this post-translational modification affects TRPM8 subcellular distribution, we investigated if S29 phosphorylation increases the degradation rate of TRPM8 ion channels by the lysosome. We generated two stable HEK293 cell lines expressing wild-type mTRPM8-myc and mutant S29A-

mTRPM8-myc channels. The functional evaluation of these cell lines reproduced our previous findings, where the S29A-mTRPM8-myc cell line exhibited higher responses to cold and menthol due to increased G_{max} and a leftward shift of the $V_{1/2}$ towards negative membrane potentials. To assess if the increase in the G_{max} could be related to a decrease in the degradation rate of TRPM8 when it is not phosphorylated at S29, we evaluated the effect of a lysosome inhibition at different times, estimating the accumulation of TRPM8 protein by western blot analysis. Our preliminary results in that regard do evidence differences between the two cell lines, suggesting that this form of modulation could have a role in the regulation of the degradation rate of this channel.

Financing: Supported by Grants DICYT-VRIIC 022143PP (MP) and VRIIC-USACH 021843MM (RM), and by the Millennium Nucleus of Ion Channel-Associated Diseases (MiNICAD) and the Millennium Nucleus for the Study of Pain (MiNuS-Pain). EM is funded by the ANID fellowship 21232288.

Visual processing in two phases of menstrual cycle

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Recent research suggests that, throughout the menstrual cycle and associated with the fluctuation of sex hormones, changes occur in the visual perception of women. Studies report better performance in emotional stimulus recognition tasks during the luteal phase, suggesting an improvement in early visual processing during this phase. On the contrary, studies that specifically use faces that express emotions have reported that the best performance in this facial emotion recognition task is observed during the follicular phase. Based on these results, it arises the question of whether the change in facial recognition of emotions throughout the menstrual cycle is caused by a general change in visual processing or by a change in emotion processing. This study examined, using electroencephalography, early visual processing and emotion recognition in faces during the follicular and luteal phase. Nineteen women with natural and regular menstrual cycles were included and recorded during the follicular phase and the luteal phase of their cycle, measured by hormonal levels. Behavioral results show a higher percentage of correct answers on the emotion recognition task and shorter response time during the luteal phase of the cycle. On the other hand, our preliminary analyses of EEG records in occipital electrodes show that the amplitude of the P100 from the visually evoked potentials (evoked by a white screen) has a bigger amplitude during the follicular phase of the cycle. Our results suggest that there is a correlation between the menstrual cycle and changes in visual perception.

Financing: Fundación Guillermo Puebla - Instituto de Neurociencia Biomédica (BNI)

Acknowledgments: Fundación Guillermo Puebla; "Centro Nacional de Inteligencia Artificial CENIA, FB210017, BASAL, ANID".

Early brain oscillatory patterns during spontaneous and evoked time windows in attentional cycling

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Mind wandering (MW) is a mental state that involves an attentional decoupling between external stimuli and ongoing tasks. At a neural level, MW has evidenced an increase in the power of high oscillatory frequencies in ventral and dorsal attentional networks (VAN - DAN), while at the same time, there is decreased power in the default mode network (DMN). However, there is contradictory evidence on the role of low frequencies as a contribution to the neural dynamics involved in the emergence of MW. For these reasons, we will describe the neural mechanisms of communication-related to low-frequency oscillations by which different attentional conditions are differentiated.

To achieve our objective, here we present the results of 9 epileptic patients with electrocortical recordings (ECoG) candidates for surgery. A modified sustained attentional task was performed to determine sustained attention conditions (ON condition) and MW (OFF condition). We used thought sampling questions (TSQ) to determine attentional states.

We found that the reaction time variability in four trials before TSQ differs between mental states. In this line, we characterize each subject's electrodes in their respective network of interest (VAN, DAN, DMN) and use a spontaneous and evoked time window to periodic and aperiodic spectral analysis of each of these networks to determine differential brain activity between conditions. We show a high-power activity in a low-frequency pattern and a decrease in aperiodic components during MW. Together, these results show novel evidence that supports the relevance of oscillatory components to explain antagonists' mental states in the same framework.

Financing: Fondecyt 1210659 Beca Doctorado Anid 21191510

Pupil Dilation: A Biomarker of Attention and a Promising Diagnostic Tool for ADHD

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Attention Deficit Hyperactivity Disorder (ADHD) stands as the most prevalent neuropsychiatric disorder among children, characterized by attention problems, impulsivity, and hyperactivity. It is linked to a deficiency in dopaminergic signaling, with the usual treatment involving dopamine/norepinephrine reuptake inhibitors. The prevailing diagnosis employed worldwide is based on observed behavior and reported symptoms, a subjective approach that leaves room for diagnostic errors.

Pupillometric analysis has been employed to explore various disorders, yielding behavioral insights into the connection between eye movements and behavior. Notably, pupil diameter emerges as a robust variable capable of distinguishing between individuals with ADHD and a control group during the working memory task, as demonstrated by Wainstein et al. in 2017. While the precise cognitive pathways that link these attentional modulations to pupil size remain unknown, this phenomenon is associated with the brain's norepinephrine (NE) system originating in the Locus Coeruleus (LC), which has significant connections with attentional networks.

Our research aims to investigate pupillary signals and behavioral variables as potential cognitive markers supporting the diagnosis of ADHD during tasks. To achieve this, we employ a comparative approach, analyzing data using two strategies. The first strategy involves canonical methods such as Support Vector Machine and Random Forest. The second strategy employs a classifier based on Transformer Neural Networks, specialized in time series analysis. While the classic classifiers yielded a maximum accuracy of 68%, the Transformer networks achieved an accuracy of 73%. These results hold promise for the future development of diagnostic tools for ADHD and warrant further exploration across other disorders.

Financing: Fondecyt regular 1230383

Bridging sensory and feedback-related signals: Understanding the occipital cortex function in arbitrary associative learning

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Arbitrary associative learning allows us to form associations between sensory information and actions. This ability relies on reinforcement to strengthen associations and predictive processing to reduce prediction errors. During the presentation of feedback a prediction is updated so that behavioral performance is improved. This information is known to be mainly processed in the medial frontal lobe.

However, how feedback-related signals influence learning, subsequent task-related neural activity and behavior is not completely understood. Moreover, accumulating evidence indicates that sensory areas also process non-sensory information. Thus, further understanding of feedback-related information in the occipital cortex, its relation to subsequent visual processing, and the computations performed, is required.

To adress this, we ask: Does the occipital cortex process feedback-related information, just like the medial frontal cortex, in a deterministic arbitrary associative learning task? And is feedback-related neural activity associated to subsequent sensory-evoked occipital neural activity of the following stimulus to be associated?

To achieve this, we recorded brain activity using 128-channel electroencephalography from 16 subjects while they performed a visuomotor associative learning task. Subjects had to learn associations between abstract stimuli and button responses by trial-and-error with deterministic feedback. Participants also performed a psychophysical control task using the same structure and stimuli as the learning task, but it did not require learning. We will analyze the power of fronto-central and occipital electrodes and the latencies and amplitudes of feedback and sensory evoked potentials.

With this work we will contribute to the understanding of non-sensory representations in the occipital cortex during arbitrary associative learning.

Financing: FONDECYT 1230383

Integration of cognitive and somatic processes during deliberation in decision-making

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Decision-making is a complex process that consists of selecting one of several alternatives that may have different outcomes. The method of evaluating such alternatives is a central topic in understanding decision-making. Other models have attempted to explain decision-making based on studies of the central nervous system at the level of the cognitive processes involved; a view that integrates cognitive processes and autonomic nervous system activity in evaluating alternatives during decision-making has been little explored. An influential theoretical approach suggests that mental simulations, based on episodic memory, which allows us to retrieve information and mentally travel into the future and mental imagery processes, make it possible to create future scenarios related to these alternatives. Concerning the above, current studies suggest that, in addition to cognitive mechanisms, specific somatic processes modulate our decisions. If so, evaluating future scenarios would involve mechanisms that integrate mental and somatic activity. We hypothesize that evaluating future scenarios during decision-making recruits changes in the ANS, whose activity integrates cognitive and somatic processes. To test our hypothesis, we assessed the pupillary dynamics of 26 participants during deliberation in a preferential decision task. We tested their relationship with mental simulation mechanisms such as memory by measuring gaze position in time and the vividness of participants' mental imagery.

Key words: decision-making, pupillometry, mental simulation

Acknowledgments: Fundación Guillermo Puelma, Laboratorio Neurosistemas, Departamento de Neurociencias, Facultad de Medicina, Universidad de Chile

Effect of Chronic Stress on Cortical Component Responses During Selective Attention to Auditory Stimuli with Background Noise

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The nervous system's limited capacity to process all surrounding stimuli prompts the necessity of selective attention. This top-down attention approach involves prioritizing a specific sensory modality for a given task, rendering other modalities temporarily irrelevant. Acting as a biological filter, this process enhances neural responses to attended stimuli while diminishing responses to unattended ones. Notably, an association has been established between cortical alpha oscillations and the inhibition of undesired sound information, such as noise, during cognitive tasks. This involves increased alpha spectral power (ERS) in central/parietal brain regions and decreased power (ERD) in temporal areas. The alpha rhythm's hypothesized role suggests it functions as a mechanism through which the brain regulates the activation of irrelevant regions, where ERS signifies inhibition and ERD indicates neural activation.

Stress emerges as a potential disruptor of this process. Stress, a response to real or perceived threats, affects homeostasis and well-being, triggering integrated responses for physiological and behavioral adaptation. The study's objective is to explore the impact of chronic stress on human auditory selective attention. Cortical alpha oscillations associated with inhibition during selective auditory attention with auditory distractions were investigated. By analyzing Electroencephalogram records in a digit-focused paradigm amid background noise, the study aims to determine how chronic stress modifies cortical alpha oscillations linked to inhibition during auditory selective attention.

Financing: Beca de Doctorado Nacional Nº 21222243

Learning to the rhythm of curiosity: oscillatory dynamics of the epistemic curiosity state

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Experiencing curiosity is a potent affective-motivational state that propels us to explore and acquire knowledge. Several studies demonstrate that what is learned guided by curiosity is better remembered, revealing that curiosity plays a role in enhancing learning. In line with these findings, neuroimaging studies report that the state of epistemic curiosity, or "curiosity for knowledge" induces the activation of reward and memory circuits. Nevertheless, there are no studies that delve into the underlying oscillatory dynamics of epistemic curiosity. Interestingly, epistemic curiosity shares characteristics with information expectancy and motivated learning, and in both cases, an increase in frontal theta power precedes their effects on learning. In this regard, the aim of our study is to investigate the oscillatory activity underlying epistemic curiosity. We recorded subjects using EEG during a trivia test and assessed their memory. Our results show higher information recall and higher frontal theta power in states of high epistemic curiosity.

Financing: Competitive Fellowship for Doctoral Studies in Chile, ANID.Doctoral Program in Neuroscience, UC, Chile.Laboratory of basic and applied neurodynamic, UC, Chile.Laboratory of Neuroscience, Cognition and Education, UCh, Chile.

Why do we lie? Effects of academic self-esteem on the use of lies in students living in Santiago, Chile

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Several studies on lies have tried to find their motivations. One hypothesis is that people lie to obtain a psychological reward, such as appearing to have a better perception of themselves. This research seeks to test whether people with high self-esteem use more lies to protect their identity. The study examines the effects of self-esteem on the number and type of lies used by 27 subjects in a self-presentation experiment. They are asked to complete the Coopersmith self-esteem test and then proceed to an experimental stage. This consists of a conversation with a confederate about themselves, with a prior assignment of a goal to be achieved during the interaction under three different conditions, to show themselves to be (a) agreeable, (b) competent and (c) no goal. A 10-minute conversation time was stipulated and, once finished, the purpose of the research was revealed and a review of the video was requested in order to identify the lies told. Analyses revealed a positive, moderate and significant correlation between academic self-esteem and the use of lies, but no significant relationships could be established between total, general, social and household self-esteem and number of lies told. No differences were found with ANOVA by gender, self-esteem levels or by goal to be achieved during the conversation. It is discussed whether the results support the proposed hy-

pothesis about a greater use of lies to protect identities with high academic self-esteem.

Financing: Concurso de Investigación para Pregrado Invierno 2023, llevado a cabo por la Dirección de Investigación de la Pontificia Universidad Católica de Chile

Acknowledgments: Extendemos nuestro más sincero agradecimiento a Eugenio Rodríguez y Marcela Osorio. Sus valiosas orientaciones, conocimientos y apoyo inquebrantable han sido esenciales para el éxito de esta investigación. Su dedicación a la educación es inspiradora. Gracias.

Why do our eardrums move when we move our eyes?

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Active perception is the phenomenon in which sensory activity results from self-initiated motor activity. It has been reported that the eardrums also move when we perform a saccade. For instance, when performing a saccade to the right, the ipsilateral eardrum bulges, while the other contracts and vice versa. Is this phenomenon dependent on visual activity? Our hypothesis suggests that this phenomenon occurs without visual stimulation since active perception is a top-down process. We recruited 20 subjects over 18 without severe visual or hearing impairment to verify our hypothesis. We then performed closed-eye and open-eye electrooculography to measure horizontal and vertical ocular saccades and tympanic movements through intra-aural microphones. Preliminary results indicate that tympanic motion still occurs even in the absence of continuous visual stimulation.

Financing: ANID-Subdirección de Capital Humano/Doctorado Nacional/2022-folio 21221549 otorgada a MEL

Facial feature perception: comparison between normal vision and simulated central and peripheral vision alterations

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Background: Face recognition is a fundamental social activity that can be compromised by vision impairment, significantly impacting quality of life. Current face recognition theories emphasize the role of critical facial features with high perceptual sensitivity (PS) in distinguishing identities. However, the influence of these features on face recognition in visually impaired individuals, as well as distinctions between central and peripheral defects, remains unclear. In this study, we investigate PS differences for critical and non-critical facial features in simulated central and peripheral visual impairments, compared to normal vision.

Methodology: Participants assessed two facial features – a critical feature (eye shape) and a non-critical feature (mouth size) – across three conditions: simulated central visual impairment (ICV), simulated peripheral visual impairment (IPV), and normal vision. A total of 39 faces were graded, and PS was quantified using the weighted Cohen's Kappa coefficient (Kw).

Results: In all conditions, participants exhibited higher intra and intergroup Kw scores for discriminating eye shape than mouth size.

Conclusion: Our findings demonstrate reduced perceptual sensitivity for both critical and non-critical features in simulated central visual impairment when contrasted with peripheral impairment or normal vision. Notably, the critical feature –eye shape– displayed significantly higher PS compared to the non-critical feature, mouth size. These results illuminate the intricate interplay between visual impairments and facial recognition, shedding light on the intricate dynamics that shape individuals' social interactions. This study marks a significant step towards comprehending the impact of visual impairments on facial recognition processes, ultimately contributing to a deeper understanding of human social relationships.

Acknowledgments: Fondo Concursable de Investigación DETEM 2022 – 570372; Iniciativa Científica Milenio ICN09_015 Proyecto ACE 210007.

Transglutaminase and Histone Aminylation: Uncovering the Role of a New Epigenetic Mark in Drosophila melanogaster

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Histone aminylation is a post-translational modification (PTM) involving the covalent bond between an amine (dopamine, serotonin) and glutamine 5 in histone H3. Histone serotonylation (H3K4me3Q5Ser) enhances the binding of the transcriptional machinery, and in vitro data suggests that it might play a role in neuronal differentiation, while in vivo evidence suggests that its reduction leads to depressive-like behaviour. Histone dopaminylaton (H3Q5Dop) has been linked to addictive behaviours. In both cases, the aminylation reaction is catalyzed by the enzyme transglutaminase 2 (TG2). Interestingly, TG2 contributes to several brain disorders including neurodegenerative diseases and CNS injury. Recent reports support that TG2 plays a role in neural development, which is still under investigation.

Drosophila melanogaster has only one TG gene. We sought to study the role of TG and the TG-mediated PTMs in fly CNS neurodevelopment and function.

Our data show a differential distribution of H3K4me3Q5Dop and H3K4me3Q5Ser in fly brains which does not fully correlate with the localization of serotonergic or dopaminergic neurons. Interestingly, head H3K4me3Q5Dop levels increase consistent with changes in TG expression during fly development.

We studied behavioural phenotypes in 2 strains globally deficient in TG expression. We discovered that TG homozygous mutants exhibit reduced lifespan, impaired startle-induced climbing behaviour, reduced locomotion, increased centrophobism (anxiety-like behaviour), and asocial behaviour. These phenotypes are accompanied by anatomical brain modifications, evidenced by structural changes in the mushroom body and the number of dopaminergic neurons.

Thus, our data support that TG and histone aminylation play a role in Drosophila neuronal development and brain function.

Financing: Supported by Fondecyt 1231556 (Jorge Campusano) and Fondecyt 1191152 (María Estela Andrés)

Acknowledgments: Special thanks to the Unit of Advanced Microscopy (UMA), at Facultad de Ciencias Biológicas PUC.

Non-Hallucinogenic Psychedelic N,N-Dimethylaminoisotryptamine (isoDMT) restores hippocampal synaptic plasticity in the learned helplessness mice model used for the study of depression.

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The mayor depressive disorder (MDD) is the most prevalent mood disorder worldwide, with cognitive effects that has been studied primarily on hippocampus and prefrontal cortex. Both patients and animal models used for the study of depression feature diminished hippocampal volume, a decreased in: density of dendritic spines, synaptic plasticity, levels of neurotrophic factors like BDNF and the expression of glutamate receptors. The use of non-hallucinogenic psychedelic compounds like N,N-dimethylisotryptamine (isoDMT) have received attention as innovative therapeutic approaches. We studied the effect of isoDMT on the Learned Helplessness (LH) murine model of depres-

sion. The mice are stressed with electrical footshocks for two consecutive days, displaying a decay on the active mobility time and escape of 55.6% in the forced swim test (control=176.8±12.4s,n=5; LH=88.3±7.4s,n=16; p<0.005) and anhedonia in the sucrose preference test only on a small subpopulation (control=80.2±10.6%,n=4; LH= 68.1±7.7%,n=12,>0.005). LH mice display an impairment on hippocampal plasticity, specifically a reduction in CA3-CA1 long term potentiation (LTP), from control (154.8±7.4%,n=5) to LH mice (120.9±2.8%,n=17,p<0.005) evaluated in brain slices at 60 minutes after theta burst stimulation (TBS). Acute isoDMT enhances LTP in control mice in a dose dependent manner (0,05µM=152.6±4.5%,n=7; 0,5µM=161.1±9.3%,n=9; 5µM=170.1±5.6%,n=8; 50µM=187.6±6.5%,n=8, EC50=5.47µM), but without modification of the baseline responses before TBS. The impaired LTP on LH mice is restored to values like control mice (control=154.8±7.4%, n=5; LH+IsoDMT=147.2± 6.44%,n=8, p>0.005) by 10 µM of isoDMT applied in the bath. These result reveals that reduction in hippocampal LTP in LH mice can be reestablished to control levels by isoDMT.

Financing: ANID 212208073 to F.G., FONDECYT 1221682 to B.C., DICYT-USACH 022343RM to P.R., FONDECYT 1161524 to B.M., DICYT-USACH 021843MM to B.M., FONDECYT 11140430 to C.R., DICYT-USACH 0211843RS to C.R.

Acknowledgments: Vicerrectoría de Postgrado, USACH.

In silico design of peptides that interfere Reelin signaling in mature neurons.

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Neural plasticity is the ability of neurons to change or rearrange their circuits and functions in response to stimulation and is essential for learning and memory. Reelin is a glycoprotein that is part of the extracellular matrix (ECM). ECM components are important for synaptic maturation and plasticity. Reelin signaling through the ApoER2 receptor has been shown to modulate plasticity. Previous research has shown that interference of reelin signaling in mature hippocampal neurons can reactivate dendritogenesis and switch synapses to an immature-more plastic phenotype. This suggests that by modulating ECM, neural plasticity can be reactivated. A rational in silico design of peptide that binds reelin better than ApoER2 can restore plasticity in hippocampal mature neurons. Here, we designed a collection of peptides that interfere with reelin-ApoER2 signaling. Our results showed an improvement in binding affinity and stability of the interaction between peptides and reelin fragments. We synthesized and characterized our first peptide, RA01, and found that it has a surprising increase in cell viability and shows no hemolytic activity. Our results demonstrate a novel possibility to interfere in reelin signaling to increase plasticity in mature neurons. Future work will continue to study reelin signaling to better understand the processes that underlie neuronal synaptic reactivation. Overall, our findings suggest that peptides that interfere with reelin signaling may be a promising new approach for treating disorders of neural plasticity.

Financing: Dicyt Asociativo 022243ALL_DAS

Anatomical and electrophysiological differences in the accessory olfactory bulb in a model of Fragile X Syndrome

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Fragile X Syndrome (FXS) is a neurodevelopmental disorder characterized by intellectual disability and difficulties in social interaction. We evidenced that Fmr1-KO mice, a FXS model that shows reduced social behavior, can detect social olfactory cues however, they seem not to be able to discriminate among them. In mice, the accessory olfactory bulb (AOB) is implied in the processing of chemical cues that trigger social and sexual behaviors. Coincidentally, AOB shows high levels of Fragile Mental Retardation Protein (FMRP) during neurodevelopment, the absent protein in the FXS. Thus, we wondered whether anatomical and/or functional differences in the AOB of Fmr1-KO mice exist.

We did not find a difference in the volume of the AOB but the volumetric ratio between anterior and posterior regions of AOB was smaller in Fmr1-KO compared to WT. Because these regions are involved in coding signals for different behaviors, this result could explain the lesser sociability of these mice. Then, we compared the electrophysiological properties of mitral cells (MCs), projection neurons of the AOB. Fmr1-KO showed a faster membrane time constant, an action potential with a higher duration and a slower rising time. In addition, with an equal injected current, the firing rate in the Fmr1-KO was lower than WT suggesting lesser excitability in MCs. Finally, inhibitory postsynaptic currents showed reduced amplitude in the Fmr1-KO, indicating MCs in this model show altered inhibitory transmission in the AOB.

In conclusion, the anatomy-physiological differences in the AOB of the Fmr1-KO mouse could partly explain their deficit in social interaction.

Financing: This study was funded by the National Agency for Research and Development (ANID) / Scholarship Program / DOCTORADO NACIONAL/2020 – 21200657 and Project FONDECYT Regular 1210069.

Physiological oscillatory signatures associated with episodic memory deficits in a pharmacological model of epilepsy

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Epilepsy is the most frequent primary brain disorder worldwide, with a prevalence of over 50 million cases and a rate of 2.4 million new cases per year. This disease is characterized by recurrent seizures, most often originated in the hippocampus, a brain structure located in the medial temporal lobe. As the hippocampus is implicated in spatial memory processes, patients with temporal lobe epilepsy (TLE) suffer, among other effects, from spatial memory impairment. The aim of the current study is to correlate hippocampal epileptogenic activity with behavioural performance in a spatial memory task. To do so, we implemented a murine model for TLE that develops hippocampal sclerosis and electrical epileptiform discharges with low seizure activity. One group of mice (n = 21) was unilaterally injected with KA in the amygdaloid complex (KA group). A second group (n = 12) was injected with saline solution (control group). Performance was assessed for both groups in a pattern separation test. Finally, animals were acutely anesthetized and bilateral hippocampal electrical recordings were acquired. The control group spent more time exploring the new object relative to the KA group (p<0.01 Wilcoxon test), suggesting that KA-injected mice could not discriminate between familiar and novel positions of the objects tested. Moreover, the density of hippocampal ictal discharges was correlated with task performance (R^2 = 0.2337, p = 0.0004, Pearson Correlation Test). Our results provide behavioral and physiological evidence to understand the substrates that underlie spatial memory dysfunctions in epileptic patients.

Financing: Fondecyt nro 1230589

Role of Ih current in the auditory cortex intrinsic excitability of a FXS mice model

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Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by an increased number of CGG repeats in the promoter region of the FMR1 gene, that

leads to the silencing of the Fragile X Messenger Ribonucleoprotein (FMRP) expression. FXS patients show auditory hypersensitivity associated to excitatory-inhibitory balance alterations in layer 2/3 and 5 neurons of the auditory cortex, determining a faulty processing of external auditory stimuli. In this regard, it has been described that in Fmr1 KO mice, the Ih current, which is sustained by HCN channels and critical to modulate neuronal excitability, synaptic integration and filter capabilities is decreased in other cortices regions. Therefore, we propose that the Ih current act as a homeostatic regulator of layer 2/3 and 5 pyramidal neurons intrinsic excitability in the auditory cortex of the Fmr1 KO mice. Using a combination of patch-clamp and immunofluorescence techniques, we found that although neurons in the Fmr1 KO auditory cortex have increased synaptic activity, they showed decreased action potential firing frequency, hyperpolarized resting membrane potential and decreased membrane resistance and sag, suggesting that a mechanism of homeostatic compensation is acting on. Additionally, we found a decreased HCN1 expression, and that the inhibition of the Ih current with ZD7288 did not reverse the changes observed in the firing frequency, nor other parameters related to the intrinsic excitability. These results show that not only Ih current contributes to homeostatic plasticity in Fmr1 KO mice, but another ion channel-mediated conductances might be involve in this phenomenon.

Financing: FONDECYT 1220680DICYT 022001CDR

Improved spatial navigation and preserved coordinated prefrontal-hippocampal activity by ATP-receptor antagonism in a murine model of epilepsy.

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Epilepsy, a disease characterized by recurrent seizures, is one of the most frequent primary brain disorders, according to the World Health Organization. Most frequently epileptic seizures are originated in a specific structure of the medial temporal lobe, the hippocampus. Although in most cases anti-seizure drugs have proven effective still, up to 30% of patients exhibit drug-resistant epilepsy emphasizing the need to find new pharmacological targets. Previous studies suggest ATP has a key role in the pathophysiology of epileptic seizures thus, we propose ATP-receptor blockade as an adjuvant pharmacological treatment for temporal lobe epilepsy (TLE). A murine kainic acid model of temporal lobe epilepsy was used, a single intrahippocampal kainic acid injection in the right hemisphere generates hippocampal sclerosis and electrical epileptogenic activity. Epileptic mice performed the metric test to assess their hippocampal function; ATP-receptor antagonist, TNP-ATP, treated mice showed better performance than non-treated animals ($p < 0.005$). Hippocampal neural activity showed decreased firing rate in right hemisphere when compared to the left ($p < 0.005$) whereas in prefrontal cortex (PFC) firing rate in the left hemisphere of TNP-ATP treated mice was lower than in non-treated animals ($p < 0.03$). Local field potential (LFP) analysis detected differences in the high frequency band of the recording both in hippocampus and PFC. Interestingly, NTP-ATP treated mice exhibited an increased LFP phase coherence between hippocampus and prefrontal cortex in theta band ($p < 0.0001$). These results suggest ATP receptors as potential targets for pharmacological treatment in combination with classic treatments for drug-resistant TLE.

Financing: N.E. and P.F. FONDECYT 1190375T.M. FONDECYT POSTDOCTORADO 3210398J.M.E Achucarro, IKERBASQUE and the UPV/EHU. S.M.S. IKUR, PID2019-104766RB-C21 (MICINN); PIBA_2021_1_0018 (Basque Government) and from Apoyo Dravet.

The intake of a high-fat diet induces sexual dimorphism in the social play of prepubertal rats

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Intake of unhealthy diets in the early life is a risk factor for mental disorders like depression and autism during childhood. The aim of this study was exploring this evidence in an animal model exposed to the intake of a high-fat diet. Adult female Sprague-Dawley rats were fed during one month with two types of normocaloric diets: control or high-fat. Females were mated with breeding males and after weaning the social play was evaluated in the offspring (females and males) during prepuberty, post-natal days (PND) 22-29. The high-fat diet did not affect maternal behavior or anxiety-like behavior in the dams compared to controls. Neurological reflexes were evaluated in the pups during the PND 3-17 to determine the impact of the diets on the development of the cerebral cortex, no differences were found between the experimental groups as well as in the locomotor activity of the pups. Interestingly, social behavior was impaired only male pups that were fed a high-fat diet relative to their controls, especially the social touch. These results suggest that male brain is vulnerable to metabolic stress induced by the intake of a high-fat diet than the female brain during the early life, affecting specific brain areas that regulates pleasure and social behavior such as the mesolimbic system. It is likely that the anhedonia or inability to feel pleasure was expressed in the male offspring through impaired social play. This study provides important insights to understand the neurobiological effects of intake an unhealthy diet during the early life.

Financing: This research was supported by FORDECYT Regular 1221098.

Sulforaphane (SFN), an activator of the Nrf-2 antioxidant pathway, ameliorate mitochondrial impairment and cognitive decline induced by hippocampal expression of caspase 3-cleaved tau

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Caspase-3 cleaved tau (TauC3) is a pathological tau modification that contributes to the pathogenesis of Alzheimer´s disease (AD). Our previous studies indicate that expression of TauC3 affects mitochondrial health inducing fragmentation, ATP loss, ROS increase, depolarization, and transport deficiencies. Mitochondrial function and the redox balance regulated by the Nrf-2 antioxidant pathway play a relevant role in synaptic communication and cognitive capacity. Here, we studied the neuroprotective effects of Nrf2 activation by sulforaphane (SFN) on mitochondrial impairment and the cognitive loss induced by TauC3 in tau knock-out (-/-) mice. Tau (-/-) mice were intrahippocampally injected with Adeno-associated (AAV) viruses containing AAV-Syn-GFP-T4 (full-length tau), AAV-Syn-GFP-T4C3 (caspase-3-cleaved tau), and AAV-Syn-GFP-P301L (tau mutation at P301L). Animals were treated with SFN and were evaluated for cognitive performance (NOR, NOL, Barnes maze tests), and mitochondrial hippocampal extracts were used to evaluate mitochondrial function. TauC3 expression affected cognitive and behavioral performance, as indicated by applying NOR, NOL, and Barnes maze tests. These adverse effects were complemented by mitochondrial dysfunction (ATP loss, depolarization, and ROS increase) induced by TauC3 in hippocampal tissue. Importantly, TauC3 mice treated with SFN (50 mg/Kg/day, two weeks) showed a significant improvement in the impaired cognitive capacity observed in TauC3 mice. These positive effects were accompanied by the improvement of mitochondrial health observed in TauC3 mice. Also, SFN treatment induced a significant increase in the expression of Nrf2-related enzymes such as TRX-1, HO-1, NQO-1, and catalase, indicating an interesting protective role of Nrf-2 pathway against neurotoxicity induced by pathological forms of tau.

Financing: ANID, FONDECYT 1200178 (RAQ)

Effect of Probenecid on pre-clinical and histological signs in Multiple Sclerosis mice models

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Pannexin-1 (Panx-1)-based channels (Panx-1-Chs) are large-pore ion channels widely expressed in the central and peripheral nervous system. Upon activation, ATP can be released through Panx-1-Chs. Panx-1-Chs activation and ATP release has been described in multiple pathological processes involving (neuro)inflammation. The use of Probenecid (PBN), an FDA approved Panx-1-Chs blocker, has been studied in several inflammatory-associated diseases. In this regard, recent evidence indicates beneficial effects of PBN in Multiple sclerosis (MS) experimental models. This pathology presents two major characteristics: (i) ubiquitous regions of the central nervous system (CNS) lacking myelin (i.e. demyelinated lesions) and (ii) local neuroinflammatory environment in those lesions. Although PBN treatment has shown improvements on MS models, the cellular mechanisms underlying these effects are not fully understood. For this reason we are evaluating the effects of in vivo PBN administration in two different demyelinating toxin-based MS models: cuprizone (CPZ) and lysolecithin (LPC) treated mice. To this end we are currently examining (1) demyelinated area (2) cellular neuroinflammatory signatures (i.e. glial cell activation) (3) Panx-1 expression and (4) locomotor performance of these mice. Our data indicates an increased expression of Panx-1 in demyelinated lesions along with an increase in the number of GFAP-positive cells (i.e. astrocytes). These changes were accompanied by a significantly decreased in the locomotor performance. We are currently analyzing the effects of PBN on these parameters; however, our preliminary data suggest a change in the Panx-1 expression pattern along with a general improvement on both pre-clinical and histological signs of the EM mice models.

Financing: Funded by FONDECYT #1210940 to FO

Relationship between Structural Connectivity and Multivariate Statistics in Neural Network Models

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Recent years have seen remarkable progress in acquiring high-quality data related to the structural (SC) and functional connectivity (FC) of the human brain networks. Comparing the network patterns and the relationship between SC and FC in healthy individuals and those with neurological disorders has revealed notable distinctions (Bassett, 2008). Traditionally, the focus has been on pairwise relationships, but emerging research suggests that interactions involving three or more elements are crucial for brain function (Mediano, 2020).

Complex network analysis provides a quantifiable approach to comprehend properties of structural networks, employing biologically meaningful measures (Deuker, 2009). Meanwhile, multivariate information theory offers tools to investigate the impact of higher-order interactions among multiple brain regions. Among these effects, statistical synergy is particularly intriguing, notably in prefrontal-parietal brain networks and higher-level cognitive tasks (Luppi, 2022).

This research explores the relationship between the topological properties of various SC networks (such as modular, hierarchical, scale-free, small-world networks, and connectome data) by assessing their levels of structural integration and segregation. The study aims to unveil how these properties affect simulated multivariate statistics on these network topologies, focusing on whether these statistics predominantly exhibit redundant or synergistic patterns.

The findings suggest that networks striking a balance between structural integration and segregation tend to display a higher prevalence of synergistic interactions. In conclusion, this study emphasizes the importance of identifying an optimal balance between network connectivity and separation to understand the emergence of complex brain interactions. This equilibrium appears to be pivotal in shaping intricate brain dynamics.

Financing: FinanciamientoFondo Institucional de Becas (FIB-UV) para el Desarrollo de Programas de Doctorado, año 2022-2023.Programa de Doctorado en Biofísica y Biología Computacional.

Acknowledgments: Agradecimientos al programa de Doctorado en Biofísica y Biología Computacional, al "Valparaíso Neural Dynamics Laboratory" (VaNDaL), al Centro Interdisciplinario de Neurociencia de Valparaíso y a la Universidad de Valparaíso.

High glucose levels trigger NTR enhancement at Drosophila Motoneuron Synapses

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Chronically high glucose levels affect the nervous system, but the effect of acutely high glucose levels on synaptic function is less known. Taking advantage that disaccharides can be intake by Drosophila neurons through sucrose transporters (SCRT) and that both sucrose and trehalose endow different amounts of glucose after their hydrolysis, we address this concern using the Drosophila motoneuron synapses. Accordingly, we evaluate the motoneuron excitatory postsynaptic current (EPSC) amplitude under voltage-clamp condition, as neurotransmitter release (NTR) indicative in the presence of sucrose and trehalose in the synapses bathing solution. Our finding shows that when glucose is supplied through trehalose hydrolysis but also under glucose itself, this synapse exhibits higher frequency of spontaneous post-synaptic currents (spsc) than when glucose is supplied through sucrose. Moreover, we found that glucose improves the NTR probability and triggers synaptic potentiation at low 0.3 Hz motoneuron nerve stimulation. Our findings also show that glucose synaptic effects were antagonized by the adenilylcyclase (AC) blocker, SQ-22536. Additionally, we found that motoneuron synapse challenged by 20 Hz stimulation under glucose exhibits synaptic potentiation in response to tetanic stimulation, while neurotransmitter NTR recovery after a 20 Hz stimulation period, either under glucose or trehalose, reaches lower levels than when synapses were fueled by sucrose. Accordingly, this result suggests a different role for glucose and fructose in this neuron. Therefore, we postulate that higher glucose levels stimulate AC, which increases synaptic vesicle (SV) availability near the NTR sites, improving the NTR probability, and consequently, enhancing the synchronic NTR.

Financing: Rersearch without funding

EEG Dynamics and Otoacoustic Distortion Products during Acoustic Residual Inhibition in Tinnitus Patients: A Pilot Study

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Introducción: Tinnitus is a phantom sound perception in the absence of stimulation, it affects quality of life and has a prevalence of up to 14% in older adults. Recent studies suggest its cerebral nature, but the neurophysiological mechanisms involved remain uncertain. **Objectives:** Our research aims to elucidate cortico-cochlear oscillatory dynamics during tinnitus using the residual inhibition paradigm, which temporarily suppresses tinnitus via broadband noise. **Material and Methods:** In this work, we are developing a case-control study with participants aged 18-50 from the University of Chile's Hospital. Inclusion criteria: chronic unilateral tinnitus (>3 months) and normal auditory thresholds. Evaluations include audiological profiles, tinnitus characteristics, and a 15-minute electroencephalographic protocol using the tinnitus residual inhibition paradigm. Subjects will be categorized into residual inhibition "responders" and "non-responders". The analysis focuses on EEG spectral power in alpha and cochlear low-frequency bands through distortion product otoacoustic emissions (DPOAE). We estimated a sample size of n=21 per group. **Preliminary results**: From three subjects we have affirmed the protocol's feasibility in capturing simultaneously EEG, DPOAE, and subjective tinnitus intensity while performing the auditory noise stimulation. **Discussion:** Evidence shows that "responders" exhibit heightened alpha band power, especially after prolonged auditory masking, but changes within the cochlear activity are still unveiled. We anticipate that residual inhibition responders will exhibit distinct cortico-cochlear changes, such as heightened EEG alpha band power linked with low-frequency changes in cochlear activity. **Conclusions:** Our results would shed light on tinnitus pathophysiology, and support the efficacy of tailored therapeutic interventions based on residual inhibition.

Financing: Fondecyt 1220607 - ANID BASAL FB0008 - Beca Doctorado Nacional ANID 2022-21221090.

Acknowledgments: Programa de Doctorado en Ciencias Biomédicas, Escuela de Postgrado, Facultad de Medicina, Universidad de Chile. Agencia Nacional de Investigación y Desarrollo, Ministerio de Ciencia, Tecnología, Conocimiento e Innovación, Gobierno de Chile.

Neural Markers of Predictive Functions in Patients with Moderate to Severe Traumatic Brain Injury

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Background: Moderate to severe traumatic brain injury (TBI-MS) is a condition characterized by cognitive impairment and psychomotor slowness, significantly impacting functional abilities. To elucidate the neural mechanisms underlying these deficits, we adopt the theoretical framework of predictive coding. According to this model, the brain generates predictions based on past sensory experiences, enabling it to anticipate future events. Electrophysiological markers, such as mismatch negativity (MMN) and P300 (comprising P3a and P3b components), offer a means to investigate these predictive processes and differentiate between various levels of information processing.

Objective: The aim of this study is to investigate whether individuals with chronic TBI-MS exhibit impairments in generating predictions at higher levels of hierarchical processing.

Methods: We recorded electroencephalography (EEG) data from 20 individuals with TBI-MS and 20 control subjects. Participants performed an auditory task known as the "global-local" oddball paradigm, which enabled us to manipulate their expectations and predictions regarding the presented stimuli. Group responses were analyzed using a non-parametric statistical approach.

Results: In individuals with TBI-MS, we observed a reduced P3b response associated with high predictive levels (clusterstat=525.9; p=0.002), in contrast to the control group (clusterstat=896.8; p=0.00009). Notably, no significant differences were detected between the groups when comparing the MMN markers, independent of attention, or the P3a marker related to attention to novel stimuli.

Conclusion: Chronic TBI-MS patients display a reduced electrophysiological response at higher hierarchical predictive levels, specifically in P3b. This observation suggests an impairment in their ability to anticipate and sustain attention in tasks requiring prolonged cognitive engagement

Financing: Chilean National Research and Development Agency ANID, FONDECYT N°11191161Ethical approval number:169-2019. Human Research Ethics Committee. Faculty of Medicine, University of Chile.

Acknowledgments: I thank Dr. Gonzalo Rivera Lillo, together with my colleagues who are part of the Project and family.

Serotonin-endocannabinoid crosstalk induces selective long-term depression at GABAergic inhibitory synapses in the medial prefrontal cortex

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Serotonergic (5-HT) fibers from the raphe nuclei are known to regulate neuronal excitability and glutamatergic synaptic function in the prefrontal cortex (PFC) by activating different 5-HT receptor subtypes (5-HTRs). However, little is known about the mechanisms by which 5-HT tune inhibitory synaptic strength in the PFC. In whole-cell patch recordings, we find that brief pharmacological activation of 5-HT2aRs induces a long-term depression of inhibitory postsynaptic currents (IPSC-LTD) onto layer II/III pyramidal neurons elicited by local electrical stimulation of synaptic inputs. 5-HT2aR-mediated IPSC-LTD is expressed presynaptically and requires the activation of type 1 cannabinoid receptors (CB1Rs). We hypothesize that 5HT2aR activation may trigger endocannabinoid production to recruit presynaptic CB1Rs to subsequently suppress GABA release. Indeed, application of CB1R agonist WIN55,212-2 also reduces IPSCs and this CB1R-mediated depression is occluded by a previous induction of 5-HT2aR-mediated IPSC-LTD, indicating a common mechanism in plasticity expression. Notably, repetitive optogenetic activation of 5-HT fibers alone is sufficient to trigger IPSC-LTD onto layer II/III pyramidal neurons that is frequency dependent and requires both 5-HT2aRs and CB1Rs. Interestingly, 5-HT2aR- and CB1R-mediated IPSC-LTD is input specific, occurring at inhibitory synapses from somatostatin- but not parvalbumin-positive GABAergic interneurons. Thus, our findings reveal a novel form of 5-HT-mediated regulation of GABAergic synaptic strength that is input-specific and strongly support a crosstalk between 5-HT2aRs and CB1Rs to modulate GABAergic inhibition in the PFC.

Financing: This work was supported by the Chilean government through FONDECYT Regular # 1201848 (AEC), # 1231012 (PRM) and FONDECYT postdoctoral grant #3190793 (RCM). CAG was supported by a PhD fellowship from ANID.

Neuronal activity in the olfactory epithelium of Fmr1 KO mice determinated through EOG.

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Fragile X Syndrome (FXS) is a neurodevelopmental disorder characterized by the absence of the Fragile X Mental Retardation Protein (FMRP). FMRP is widely expressed in the rodent brain in the somatodendritic domain of virtually all neurons. In the olfactory system, it is expressed throughout brain regions that process olfactory information, including the olfactory epithelium, bulb, and cortex. Individuals with FXS can present severe behavioral disturbances, including hyperactivity, impulsivity and anxiety, and hypersensitivity to sensory stimuli, a matter that directly influences their behavior. Fmr1 KO mice exhibit alterations in the detection threshold and discrimination of odorants, which are produced, in part, by physiological dysfunctions in the olfactory bulb and cortex. However, it is unknown whether the differences in the coding of olfactory information could also be caused by alterations in the activity of olfactory sensory neurons at a peripheral level. In order to answer whether there are differences in the neural activity of olfactory sensory neurons, we made electroolfactogram (EOG) recordings in Fmr1 KO and WT mice in response to exposure to different concentrations of odorants. Our preliminary results indicate that the neuronal response amplitude of Fmr1 KO mice is smaller compared to that of WT. This suggests that the alteration in olfactory perception includes a peripheral component. These results will help to understand more completely the neurobiological basis of this syndrome.

Somatosensory receptors in the tongue of birds with different feeding habits.

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Birds use their beak and tongue for behaviors such as feeding and object manipulation, and behavioral diversity across avian taxa is reflected in the morphological diversity of these organs. Mechanosensory receptors of the avian tongue have only been studied in a few species. Granivorous estrildid and fringillid finches possess lingual dermal papillae containing an arrangement of Herbst corpuscles (equivalent to mammalian Pacini receptors) and Grandry corpuscles (equivalent to Meissner corpuscles). These likely mediate seed shelling, which these birds perform in the oral cavity. Description of lingual receptors in further avian taxa is needed to understand whether and how the organization of the tongue touch receptors varies across birds with different feeding behaviors.

We aimed to explore the diversity of avian tongue mechanoreceptors by studying their morphology and distribution in birds with different feeding habits. We examined the tongue of an estrildid finch (Taeniopygia guttata), two psittacids (Melopsittacus undulatus and Myiopsitta monachus), and the chicken (Gallus gallus). To reveal the location of mechanosensory corpuscles in the tongue, we performed intraperitoneal injections of the activity-dependent fluorescent nerve terminal probe AM1-43.

We found striking differences in the organization, number and distribution of mechanosensory papillae across species, even between the two psittacids. The tongue of G. gallus, a granivorous species that does not shell seeds, did not exhibit mechanosensory papillae.

Our results point to a large diversity in the avian tongue somatosensory system and suggest that the number and distribution of mechanoreceptors is associated with the type of feeding behaviors.

Financing: proyectos Fondecyt regular 1210069 y Fondecyt de Iniciación

11180266.

Acknowledgments: Agradecimientos al Laboratorio de neurobiología y biología del conocer de la Universidad de Chile y al Laboratorio de Evolución y Desarrollo de la Pontificia Universidad Católica de Chile.

Cortical Dynamics during reversal learning in a spatial memory task.

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Spatial learning is a complex cognitive process that integrates multiple brain areas. During task execution, animals learn and adapt through trial-and-error, refining their choices based on outcomes. This iterative process involves integrating internal and external information within the brain, fostering adaptive decision-making to optimize selections within dynamic changing environments.

The hippocampus holds a central role in this framework, constructing representations of the environment, spatial locations, and their contents, thereby supporting spatial memory and versatile navigation. Anatomical connections link the hippocampus with the prefrontal and retrosplenial cortices, critical for navigation and spatial learning. The prefrontal cortex supports context-spatial decision-making, whereas the retrosplenial cortex facilitates the shift between egocentric and allocentric reference frames.

This study investigates neural dynamics by recording activity in the hippocampus (both ventral and dorsal), retrosplenial cortex, and prefrontal cortex in freely moving rats during the execution of a reversal learning task. Our analysis reveals significant changes in transient cortical connectivity associated with task performance.

These findings provide a comprehensive overview of the neural mechanisms of spatial learning, shedding light on the intricate network dynamics associated with the execution of cognitive tasks and decision making in real-world environments.

Financing: Proyecto Fondecyt 1230589

Optimization of PC12 Cell Line Expansion for an In Vitro Model of Cerebral Ischemia

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Introduction: In vitro ischemia are crucial for pathophysiology studies and therapy evaluation. This study compared two expansion methods for PC12 cells and evaluated their response in an ischemic environment. Objective: Develop an expansion protocol for the PC12 cell line and establish an in vitro ischemia model. Methodology: We worked with the PC12 cell line acquired commercially from ATCC and tested two cell expansion protocols with different dissociations. Cultures were evaluated by using light microscopy and using ImageJ to assess cell counting. The ischemia model involved cultures exposed to environments without glucose and oxygen, LDH assay were used to measure viability. Results: The area occupied by the cells in the images and the size of the clusters in each protocol were evaluated. It was observed that, on average, on days 1 and 5, the area occupied by cells was significantly smaller in 5 times dissociation cultures compared to 10 times dissociation cultures. Regarding the size of the clusters, differences were found between protocols on day 5, which showed a larger size. For both protocols, 1x10^6 cells were seeded on day 0. With respect to the ischemic model, cultures subjected to 3 hours of anoxia and hypoglycemia showed mortality. Conclusions: The growth of the PC12 cell line was optimized. In 3 hours were needed to access an in vitro ischemia model.

Acknowledgments: Dr. Roland Gittens, Dr. Bernardino Denis

Demyelination of PreBötC reduces the ventilatory response induced by hypercapnia.

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Central respiratory chemoreception is fundamental for the generation and modulation of the respiratory rhythm, allowing breathing to be adjusted to the physiological demands by the function of multiple interconnected nuclei in the brainstem. One of these nuclei is the pre-Bötzinger complex (preBötC), a small nucleus that is critical for the generation of inspiration. The myelin is a specialized membrane produced by oligodendrocytes in the CNS. It has been proposed that myelin contributes to the regulation of neural excitability. However, the functional impact of myelin in the respiratory rhythm has not been studied. Here, we addressed whether the myelin damage restricted to the preBötC impacts the respiratory function. So, we injected lysolecithin (LPC, a myelin-destroying toxin) into the preBötC of 21-day postnatal CF1 mice. The effects on the preBötC were analyzed using immunohistochemistry, local field potential recordings, and whole animal plethysmography after 7 days post-injection. Preliminary results suggest that confirmed local demyelination lesions in the preBötC by Immunohistochemistry increases basal respiratory frequency in acute brainstem slices, suggestive of a higher excitatory status. In addition, plethysmography studies revealed that demyelination reduces the increases in respiratory frequency, minute volume, and tidal volume in response to hypercapnia compared to those observed in controls. Finally, in complementary results, the increases in respiratory neural circuit excitability reduce the response to hypercapnia compared to control. These results highlight the relationship between neural excitability, chemoreception, and myelin in a physiological context.

Financing: Supported by Fondecyt 1211359 (JE) and Fondecyt 1210940 (FO)

POSTER SESSION II

The expression of the endocannabinoid system, a signaling system widely expressed in nature, is regulated by extracellular glucose.

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The Endocannabinoid System (ECS) is a cell signaling system widely present in nature. Its main components are CB1R and CB2R receptors, as well as a group of enzymes for the synthesis and degradation of endocannabinoids such as 2-arachidonylglycerol acid (2-AG) and anandamide (AEA). Using data generated by our and other laboratories, it is possible to affirm that the ECS is quite conserved in structural and pharmacological terms. For example, molecules such as THC, the main active compound present in Cannabis sativa, a quite specific CB1R agonist, have been shown to produce an orexigenic effect characterized by increasing food intake in many different animal species. Moreover, this receptor possesses highly conserved critical amino acids evolved in structural stability, molecular function associated with G-protein activation, and binding of different types of ligands such as the cannabinoid CBD. Finally, other critical molecules such as glucose have been shown for our lab to be a critical regulator at the level of ECS gene expression in relevant organs for proper animal function. For example, using a highly reproducible experimental model to increase blood glucose in 5-7 animals, in 6 independent replicates, 3 of these from different animal generations we have shown that extracellular glucose produces a strong regulation of ECS expression in mice and or rats organs or tissues relevant to energy balance such as the brain, liver and skeletal muscle, a situation that has not been described to date.

Financing: Funding information. Fondecyt Iniciacion 11150992, Fondecyt Regular 1180871, Proyecto Redes REDI17

Acknowledgments: Agradecimientos sinceros de manera postume al trabajo realizado por la Dra (c). Alejandra Elizabeth Palma Chavez, quien falleciera víctima de femicidio en Concepción el 8 de marzo de 2023.

Differential contribution of residues Y745, D802 and R842 in the TRPM8 response to chemical agonists

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TRPM8 is the main molecular entity responsible for detecting cold temperatures in the somatosensory system. This ion channel is activated by cold, cooling compounds such as menthol, voltage, and osmolality rises. TRPM8 is also involved in several pathologies, including cold hypersensitivity in response to axonal damage, dry-eye disease, migraine, overactive bladder, and several forms of cancer. In this scenario, therapies focused on the TRPM8 modulation could be an alternative for their treatment. Since the clinical use of known agonists and antagonists has faced several problems, developing novel modulators of TRPM8 function is critical. However, the rational design and the high throughput virtual screening that could be helpful strategies in this task require a comprehensive understanding of how agonists and antagonists modulate TRPM8 activity.

To this end, we built a comparative model of human TRPM8 and identified relevant residues for the binding of the TRPM8 agonists menthol, WS-12, and icilin using molecular docking, molecular dynamics simulations, and binding free energy calculations. Our analysis showed that Y745, D802, and R842 contribute significantly to the binding of these compounds. To experimentally validate their involvement, we mutated these three residues and evaluated the impact of these mutations on the TRPM8 responses to these agonists using Ca^{2+}-imaging analysis. Our results show that most of the mutants of these positions displayed different effects on their responses to WS-12, icilin, and menthol without significantly altering their cold activation, providing critical clues about the specific contribution of each residue in the TRPM8 activation by these compounds.

Financing: Supported by Grants DICYT-VRIIC 022143PP (MP), VRIIC-USACH 021843MM (RM), and FONDECYT 1230999 (JAM and JR), and the Millennium Nucleus of Ion Channel-Associated Diseases (MiNICAD) (MP, RM) and the Millennium Nucleus for the Study of Pain (MiNuSPain) (MP, RM). MV is funded by ViPo-USACH and JS by ANID fellowship 21201001.

Studying the role of 5-HT6 receptor on nLSD1/LSD1 ratio

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In recent years, the serotonin 6 receptor (5-HT_6R) has attracted great attention due to its role in neurodevelopment and cognitive processes. Belonging to the GPCR family, 5-HT_6R has a large mRNA expression throughout the CNS, mainly in nuclei such as the striatum, hippocampus, and cortex. Recently, it was shown that 5-HT_6R stimulation modifies the epigenetic state of postsynaptic neurons, regulating chromatin accessibility. Furthermore, 5-HT_6R interacts with the neuro-oncogene ventral antigen 1 (Nova-1), a neuro-specific splicing regulatory factor, modifying its traffic and target genes. Based on these findings, our study seeks to evaluate the impact of pharmacological modulation of 5-HT_6R using PUC-10, an antagonist synthesized by our group. PUC-10 shows a high affinity (K_i=14,6 nM) and potency (IC_{50}=32 nM) on 5-HT_6R. We are studying if PUC-10 blocks the effect of 5-HT on Nova-1 trafficking from nucleus to the cytoplasm of the cells using SH-SY5Y and primary cultured neurons. In addition, we are studying the expression of neuronal lysine-specific demethylase 1 (neuroLSD1), a target of NOVA-1.

Our data show that the ratio between the transcripts of neuroLSD1 and the unspliced isoform (neuroLSD1/LSD1) is closed to 1:1, in basal conditions in SH-SY5Y; like several brain nuclei such as the striatum and hippocampus.

Financing: Proyecto Puente UC to María Estela Andrés Coke

Strategy to identify neuroLSD1 specific proteome

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LSD1 is an epigenetic enzyme that regulates transcription by demethylation of mono and dimethyl lysine 4 of the histone H3 (H3K4me1/2), acting as a repressor of target genes. LSD1 has a neuro-specific isoform, neuroLSD1 (nLSD1), associated to cognitive and emotional regulation. This variant is generated by alternative splicing, allowing the inclusion of the microexon E8a, a sequence of 12 nucleotides that encodes for an Asp-Thr-Val-Lys microdomain. LSD1 isoforms regulate the transcription of immediate early genes (IEGs) in opposite way. While LSD1 represses the expression of IEGs, nLSD1 enhances it. This seems possible because nLSD1 has other substrates, demethylating H3K9me1/2 and H4K20me1/2, instead of H3K4me1/2. It was reported that when the threonine in the microdomain is phosphorylated, CoREST and HDAC1/2 are detached from nLSD1, decreasing its repressive activity. On the other hand, nLSD1 interacts with supervillin (SVIL), gaining H3K9me1/2 demethylase activity. However, our coimmunoprecipitation data showed that SVIL interacts with both isoforms. To better understand how nLSD1 gains hi-

stone substrate specificity, we aim to identify the proteome associated with its microdomain. To this end, we have built flag-tagged fragment of nLSD1 containing the microdomain plus a nuclear localization signal, and a phosphomimetic mutant for regulatory threonine. Our results show that recombinant peptides expressed correctly and locate in the cell nuclei. Using the crystal structure of nLSD1 and structural analysis softwares, we will study how phosphorylated/unphosphorylated microdomain may modify protein-protein interactions. Immunoprecipitation of nLSD1 fragments and mass spectrometry analysis will allow us to identify the proteins associated with the microdomain.

Study of the effect of acute and repeated amphetamine on substrate epigenetic marks of Lysine-specific demethylase in mice brain

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LSD1 is an enzyme that demethylates H3K4me/me2, an epigenetic mark associated with active transcription. As a result, LSD1 functions as a co-repressor of gene expression. This enzyme has a neurospecific isoform (nLSD1) that plays a dominant-negative function concerning the ubiquitous isoform (uLSD1). Furthermore, nLSD1 demethylate H3K9me/me2 and H4K20me/me2, marks associated with gene repression. uLSD1 and nLSD1 coexist in the brain in a similar proportion. Under neuronal activity, there is a change in the uLSD1/nLSD1 ratio, with an increase in uLSD1 and a concomitant decrease in the nLSD1 isoform. This study aims to determine changes in LSD1 variants substrates (H3K4me2, H3K9me2, and H4K20me2) in the mouse brain after acute and repeated administration of amphetamine. The acute administration evaluates total LSD1 and their substrates through Western blot at 2-, 8-, and 24-hours post-injection in naive mice. We assessed the alteration in total LSD1 and its substrates using immunofluorescence 7 hours after the acute administration of amphetamine in wild-type mice and nLSD1 knockout mice. For repeated administration of amphetamine, nLSD1 WT and KO mice were injected with four doses of amphetamine. Twenty-four hours after the last injection, total LSD1 and substrates were assessed. Western blot results we obtained indicate that the act of injection itself significantly impacts LSD1 and H3K9me2 levels. Additionally, we observed that both acute and repeated administration of amphetamine does not induce alterations in LSD1 levels and its substrate within the hippocampus and striatum. However, the immunofluorescence findings offer hints of a potential impact of amphetamine on the knockout mice.

Financing: Proyecto Puente to María Estela Andrés

The neuronal Drosophila melanogaster Monocarboxylatetransporter Small Chaski is induced by starvation and itsdownregulation associates to functional defects.

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The provision of energy is required for the proper functioning of the brain, which is primarily occupied with the maintenance of synaptic processes. Energy is obtained in neuronal cells via glucose transporters and monocarboxylic acid transporters (MCT), which transport metabolites such as lactate and pyruvate directly into the tricarboxylic acid cycle, allowing energy to be obtained more quickly than glucose. MCTs are encoded by 15 genes in Drosophila, indicating functional redundancy. Some of the genes investigated can respond to various environmental situations such as stress or malnutrition. We focused on the gene CG8389, also known as small-chaski (schk), which is activated in neurons during starvation. schk is expressed in neurons, including larval NMJ motor neurons. We used dsRNAi to downregulate its expression in this glutamatergic synapse and noticed a decrease in active zones, the formation of phantom buttons, and functional issues in the neuromuscular synapse, such as abnormalities in the spontaneous release of neurotransmitters. Furthermore, schk-deficient flies showed impairments in motility, viability, and survival in larvae and adults. These findings point to a critical function in the preservation of synaptic function in the nervous system of Drosophila melanogaster.

Financing: Fondecyt Regular 1210586, Instituto de Neurociencias Biomedicas (BNI)

The LSD1/nLSD1 ratio as a modulator of gene transcription involved in the development and persistence of compulsive behaviors

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Compulsive behaviors (CBs), i.e. maladaptive patterns of repetitive behavior and inflexible cognition, are features associated with mental health conditions such as addiction and obsessive-compulsive disorder (OCD). Several altered neural systems have been identified, including the mesocorticolimbic dopaminergic system. Recently, an epigenetic role in the perpetuation of CBs has been considered. LSD1, a histone demethylase enzyme, and its neuronal isoform, nLSD1, remove mono- and dimethylations at lysine residues in histones, having opposites effects on transcription of target genes. The LSD1/nLSD1 ratio has been proposed as a sensor to environmental signals, modulating the transcriptional activity of genes relevant to the development of CBs. Among some genes identified as targets of LSD1/nLSD1 are the so-called immediate early genes (IEGs).

There are animal models characterized by the appearance of stereotyped CBs. Validated pharmacological models of OCD and addiction can be induced by repeated administration of quinpirole (QNP), a dopamine D2/D3 receptor agonist and the psychostimulant amphetamine (AMPH), respectively. We propose that LSD1 acts as an epigenetic factor in the appearance of these behaviors. Our results indicate an altered expression of IEGs in rat brain after repeated administration with QNP and AMPH. Specifically, c-Fos and Arc IEGs are decreased by QNP treatment and Fos-b is increased by both treatments in the hippocampus. The expression products of these genes are associated with neuronal plasticity and may be relevant in the perpetuation of CBs. Simultaneously, efforts are being made to identify other LSD1 target genes by bioinformatic analysis of gene expression in public databases.

Financing: Proyecto Puente UC to María Estela Andrés

Relation between ocular scanpath and facial expression recognition in children with social deficitspant performance.

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Many childhood disorders, such as Anxiety Disorder (AD) and Attention Deficit Hyperactivity Disorder (ADHD), are marked by poor emotion recognition and social difficulties, but it remains uncertain whether these arise from deficits in visual scanning strategies or mainly from visual content processing. AD are characterized by persistent feelings of worry and nervousness in response to stressors, impacting the overall functioning. ADHD features persistent patterns of inattention and hyperactivity that disrupt cognitive and adaptive abilities. These disorders share social difficulties, manifesting as limited social competence, leading to emotional dysregulation that affects perception and recognition of emotions. The coexistence of AD and ADHD leads to heightened emotional distress and diminished social skills; they display higher error rates in emotional recognition tasks and a visual scanning different from healthy controls. Moreover, evidence shows that children with AD , and also children with ADHD, exhibit lower fixation concentration on emotion recognition tasks. But, evidence from gaze behavior from ADHD and AD is lacking. In this work, we hypothesize that the child and adolescent population with ADHD/AD engage in visual scanning of faces with brief fixations and more scattered over the image, resulting in inefficient emotional expression processing. To investigate this, we evaluate the visual scanpath of 12 children/adolescents with AD and/or ADHD while performing an emotion recognition task. Our preliminary results suggest that participants' performance improves with age, regardless of the specific diagnosis. Further analyses are needed to determine the role of visual fixation on participant performance.

Financing: Beca Puelma

Acknowledgments: PUELMA, "Centro Nacional de Inteligencia Artificial CENIA, FB210017, BASAL, ANID"

The pupil as a window to cognition: study of attentional shift during visual exploration

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Abstract

Background: The pupil, situated at the eye's center within the iris, regulates light intake for retinal phototransduction. Its size modulation, influenced by diverse factors including motor, emotional, and cognitive components like attention, has been extensively studied. Despite diverse models, a comprehensive understanding of attention within ecologically valid contexts remains elusive. This study aims to bridge this gap, exploring pupil dynamics and attention during naturalistic visual exploration, shedding light on the intricacies of attention in real-life scenarios. **Methods:** Employing a free visual exploration task with 30 natural images, resembling everyday scenes, participants explored images while pupil diameter and eye movements were tracked. **Results:** Upon saccadic eye movement onset, a pronounced pupillary constriction emerged, stabilizing around 0.6 seconds in relation to the original pupil's diameter. At the 2-second mark, substantial diameter differences surfaced between short and long saccades. Notably, short saccades exhibited around 20% more dilation during later stages of eye movement performance. **Conclusions:** Late-stage variations in pupil size, identified in our study, may stem from pre-eye movement fluctuations. This underscores our proposition of these results as a pupillary response influenced by gaze movement anticipation. These findings provide insights into the intricate interplay between attention, eye movements, and pupil dynamics in an ecologically meaningful context, advancing our comprehension of real-life attentional processes. **Keywords:** Pupil, Attention, Visual examination, Cognition, Eye movements

Acknowledgments: Fondo Concursable de Investigación DETEM 2022 – 570372; IniciativaCientífica Milenio ICN09_015 Proyecto ACE 210007.

Neuronal Correlates of Innate Fear Expression: Interoceptive Insular Cortex Activity during Rat Freezing Behavior

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The insular cortex (IC) plays a role in the monitoring of bodily and emotional responses of animals. Previous research demonstrated that the interoceptive region of the insular cortex (pIC) is involved in expressing both innate and conditioned fear responses measured by freezing behavior. However, how the pIC encodes changes in response to a natural threat remains unclear. Here, we used electrophysiological recordings of single units in behaving male rats exposed to a cat odor to investigate the pIC contribution in the innate fear in rats, as measured by time spent on freezing behavior and the duration of freezing episodes. We observed differences in how pIC encodes interoceptive information about fear levels across individual fear responses, comparing high-fear (HFS) and low-fear states (LFS) and long and short periods of fear. Our analysis revealed that a subset of units modulated their firing rate (FR) during freezing behavior, observed in both the HFS and LFS groups. Notably, distinct patterns emerged within these states, indicating a rapid and sustained pattern in responsive units during prolonged freezing periods in HFS rats compared to LFS rats. Furthermore, we showed a significant reduction in the number of long freezing episodes following pIC inactivation, which was corroborated by the positive correlation between the number of such episodes and their FR along the behavior. Together, our findings show the crucial role of pIC neuronal activity in the maintenance of fear responses, suggesting its involvement in sustained fear processing.

Financing: Support by Fondecyt 1130042 and Postdoctoral Fellowship UOH

Characterization of locomotor behavior in a Drosophila mutant for a new signaling molecule, Drospondin

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Reelin is an extracellular vertebrate glycoprotein fundamental in brain development, where it is responsible for neuronal migration, cerebral cortex and hippocampal patterning. It has also been associated with neuronal plasticity in the mature brain. Dysregulation of Reelin expression has been linked to several neuropsychiatric disorders such as schizophrenia, autism, and Alzheimer's disease. In mice, a spontaneous recessive mutation leads to the Reeler phenotype characterized by ataxia, tremors, hypotonia and unsteady gait, due to an abnormal structure organization of cerebral cortex, hippocampus and cerebellum. Through sequence homology analysis, our research group proposed a previously uncharacterized protein in Drosophila melanogaster genome, as a reelin-like protein. We named it Drospondin. Our data show that as mammalian Reelin (mReelin), Drospondin is a secreted glycoprotein which induces an increase in neurite complexity in primary Drosophila neuronal cultures. Our data also suggest that Drospondin expression is essential in fly brain anatomy. In this regard, deficits in Drospondin expression result in anatomical phenotypes in a bilateral Drosophila brain structure essential for olfactory learning and memory, and fly locomotor activity, the Mushroom Body. Here, we aimed to characterize the locomotor behavior of Drospondin mutants over aging, by the evaluation of different parameters. Our hypothesis is that Drospondin deficiency results in locomotor deficits similar to those observed in Reeler mutants.

Financing: This study was supported by Fondecyt grant 1200393 to María Paz Marzolo and Fondecyt grant 1231556 to Jorge M. Campusano

Frontoparietal contribution to the construction of conscious visual representations and its relationship with perceptual confidence

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Consciousness as content refers to those self-reported experiential instances, understood as 'awareness'. According to the Global Neuronal Workspace Model, perceptual awareness depends on fronto-parietal network activation. In contrast, Neural Identity Theory aims to address the ontological status of phenomenality. Evidence suggests the contribution of frontal activity for awareness, while fMRI experiments indicate brain representations for perceptual content. Considering both frameworks, it is unclear if there is a neural representation for perceptual content related to frontal regions. Regarding this, frontal regions are related to confidence representations, while perceptual content has been related to the posterior. This research aims to determine the frontoparietal contribution to the construction of conscious visual representations and its relationship with perceptual confidence. We collected fMRI data from 26 participants who performed a Shadlen Random Dot Motion (RDM) task. Reportability (objective rating) and perceptual confidence (subjective rating) were evaluated in at least 160 trials. Two fMRI analyses were performed. Desikan-Killiany atlas was used to perform 1.ROI analysis under different conditions (direction, perceptual threshold, confidence). 2.Multivoxel Pattern Analysis to decode brain activity, picking the most accurate voxels. If there is something such as frontal neural representation for awareness, it is expected a higher percentage of accurate voxels when the participant is aware of specific contents. It is observed that representation was significantly more encoded in right fronto-parietal areas than occipital when stimuli were below consciousness threshold. While left-frontal activity contributes more to objective rating, confidence, and stimuli coherence. This suggests a topographic encoding on the anteroposterior axis.

Financing: FONDECYT 1171320 FONDECYT 1230383ANID SCHOLARSHIP 21191357 Data collection and sharing for this project was provided by the

DecNef Department at the Advanced Telecommunication Research Institute International, Kyoto, Japan.

Acknowledgments: Agradecimientos a Catalina Saini, por su colaboración en la recolección de datos. A María Paz Araneda y Gabriel Quintana por participación en espacios de discusión

Hunger enhances hippocampal memory consolidation during wakefulness

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Recent evidence challenges the widely accepted notion that sleep is required for memory consolidation, as non-hippocampal dependent memories have been reported to consolidate during sustained wake after memory acquisition. Here, we present evidence that hunger contributes to consolidating hippocampal dependent memories without sleep occurring during the critical window of memory formation.

Eleven adult Sprague Dawley male rats under standard light-dark cycle conditions were evaluated for their performance on the Object in Place Recognition test (OPR) under ad libitum, 24-h, and 48-h fasting conditions while they were either sleep-deprived or not after learning. In addition, four of these rats were electrophysiological and polysomnographic recorded during the fasting and sleep deprivation period, which has allowed us to characterize the architecture of the sleep-wake cycle to further explore the neurophysiological properties of sleep and wakefulness during sleep deprivation under fasting and ad-libitum conditions.

The performance on the OPR task was similarly efficient under both control (ad libitum/ non-sleep deprived) and the 48 hours of fasting combined with sleep-deprivation conditions. These results suggest that hunger may potentiate hippocampal-dependent memory consolidation processes during wakefulness. Our results are a starting point to explore the physiological mechanisms involved in hippocampus-dependent memory consolidation during wakefulness in adverse survival conditions such as food scarcity

Acknowledgments: Pew Innovative Founding. Fundación Guillermo Puelma.

The Effects of Brain Oscillation-Stimulated Cognitive Training Therapy in Patients with Mild Cognitive Impairment: Preliminary Results

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The increasing prevalence of disabling conditions such as Dementia and Mild Cognitive Impairment (MCI) due to an aging population necessitates the development of effective interventions. MCI represents a critical stage for preserving cognitive function. Working memory (WM), a fundamental aspect of executive functions and long-term memory maintenance, plays a central role in this preservation. In this study, we present preliminary results of a protocol aimed at enhancing WM in individuals with MCI through cognitive training and transcranial electrical stimulation of alternating current (tACS), a non-invasive brain stimulation technique. Recent findings have demonstrated the potential of cognitive training to improve WM, while tACS has shown promise in inducing neural plasticity. The intervention, a Phase IIb randomized, single-blind clinical trial, spanned three months and involved participants diagnosed with MCI, aged above 60. The intervention consisted of twelve training sessions combined with tACS, with participants randomly assigned to receive either active tACS or placebo stimulation in eight sessions. The study's primary outcomes included the assessment of prefrontal theta oscillatory activity using electroencephalography, while secondary effects involved evaluations of WM cognitive performance. Participants underwent assessments before the intervention, immediately after the intervention, and three months later. Preliminary results demonstrated increased working memory performance in both groups. However, participants who received active tACS showed greater improvements in cognitive performance and exhibited a reorganization of their oscillatory activity in the theta band. The trial's final results will provide empirical evidence regarding the feasibility and benefits of combining cognitive training with non-invasive brain stimulation (NCT05291208).

Financing: ANID: proyecto FONIS SA19I0118

A causal role for the lateral prefrontal theta oscillation in the expectancy of conflicting stimuli

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Subjects can anticipate conflictive situations, learning from the environment. Proactive cognitive control integrates the experience, building a conflict expectancy that allows them to elaborate adaptive responses. Frontal theta activity is associated with cognitive control, and proactive cognitive control is associated with the dorsolateral prefrontal cortex. We hypothesize that theta activity in the lateral prefrontal cortex plays a causal role in conflict expectancy. We used fMRI to identify candidate brain areas associated with proactive cognitive control, EEG to measure brain electrical activity, and TMS to study a causal relationship between brain oscillations and cognitive activity. Fifty-nine healthy adults participated in 3 experiments. Using computational cognitive modeling in behavioral data, we found that conflict expectancy significantly slows the reaction time during go stimuli. Using fMRI, we found that conflict expectancy correlates with brain activity in the superior frontal gyrus (SFG), while the inferior frontal junction (IFJ) was associated with conflict stimuli. Finally, using TMS, we found that only theta stimulation over SFG increased the slowness of reaction time related to conflict expectancy. EEG activity reveals that this effect was corrected with increased theta activity in baseline after TMS stimulation. Therefore, SFG is involved in computing the expectancy of conflicting events through theta oscillations. This oscillatory activity in the lateral prefrontal cortex is causal in conflict expectancy.

Financing: This work was supported by Agencia Nacional de Investigación y Desarrollo de Chile (ANID), FONDECYT (1181295 and 1211227 to P.B.), PAI (PAI77190047 to P.S-I), FONDEQUIP EQM150076.

Characterization of Retinal Ganglion Cell topography during ontogeny of the Chilean endemic rodent Octodon degus

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In all vertebrate's, retinal ganglion cells (RGCs) distributed anisotropically in the retina, forming retinal specializations which are distinctively related with the visual habits of each species. An unresolved problem is how these specializations arise during ontogeny.

We studied the postnatal development of RGCs anisotropies in Octodon degus, a highly visual, diurnal, precocial native rodent exhibiting conspicuous reti-

nal specializations. Retinal wholemount were prepared from P04 to the adult stage and Nissl stained (n=14). Cell counts were performed using the optical fractionator method. Subsequently, topographic maps were generated using a script in R.

We found that RGCs maintain a constant average number of (about 300.000 cells, counting RGCs plus displaced amacrines) from P04 onwards. As the retina develops, its surface area doubles (from 48.39 to 90.28 mm^2), while the density of RGCs decrease to a half of its initial value (from 7.569 at P04 to 3.576 cells/mm^2 at adult stage). Furthermore, at P04, no clear specializations were observed. These specializations begin to emerge from P14 and consolidate at P30. At this stage retinas present several adult specializations, such as a ventro-dorsal gradient, an area temporalis, and a visual streak in the naso-temporal axis.

Our results expose the complex process of postnatal development of the O. degus retina, which seems to involve a considerable rearrangement of RGC densities, presumably caused by a non-uniform growth of the retina. This phenomenon occurs while the animal is actively engaged in its visual environment, suggesting a crucial role of visual experience in sensory maturation.

Financing: Fondecyt 1210169 Fondecyt 1210069

Acknowledgments: Thanks to Elisa Sentis and Solano Henríquez for their technical support.

Improved synaptic plasticity by a peptide that interferes with the reelin signaling in mature hippocampal neurons.

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Neural plasticity is the ability of neurons to change or rearrange their circuits and functions in response to stimulation and is essential for learning and memory. Reelin is a glycoprotein that is part of the extracellular matrix (ECM). ECM components are important for synaptic maturation and plasticity. Reelin signaling through the ApoER2 receptor has been shown to modulate plasticity. Previous research has shown that interference of reelin signaling in mature hippocampal neurons can reactivate dendritogenesis and switch synapses to an immature-more plastic phenotype. This suggests that by modulating ECM, neural plasticity can be reactivated. A rational in silico design of peptide that binds reelin better than ApoER2 can restore plasticity in hippocampal mature neurons. Here, we designed a collection of peptides that interfere with reelin-ApoER2 signaling. Our results showed an improvement in binding affinity and stability of the interaction between peptides and reelin fragments. We synthesized and characterized our first peptide, RA01, and found that it has a surprising increase in cell viability and shows no hemolytic activity. Our results demonstrate a novel possibility to interfere in reelin signaling to increase plasticity in mature neurons. Future work will continue to study reelin signaling to better understand the processes that underlie neuronal synaptic reactivation. Overall, our findings suggest that peptides that interfere with reelin signaling may be a promising new approach for treating disorders of neural plasticity.

Financing: Dicyt Asociativo 022243ALL_DAS

Stimulation of the somatostatin-expressing inhibitory interneurons increases the structural plasticity and reduces the cognitive decline during aging.

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Aging is a natural process that affects our brain and memories. The hippocampus, a key brain region for learning and memory, undergoes changes during aging, such as a decrease in the number of synapses, or connections between neurons, it more difficult to form new memories. The balance between excitatory and inhibitory neurotransmission is crucial for the formation of new memories, and interneurons (INs) are essential for controlling this activity. Among these, somatostatin-expressing interneurons (INs-SST) are essential, particularly within the dentate gyrus (DG) and hilus regions which are in higher proportion. In the hilus, INs-SST synapse with granule cells (GC) during memory encoding. It is hypothesized that the activation of INs-SST in the DG improves structural plasticity and memory in aged mice. Our results shown that the number of INs-SST decreases in the hippocampus of aged mice. It was analyzed whether the stimulation of the INs-SST activity decreases the cognitive deficit that is observed in aged subjects improving the structural plasticity. Were used cre-SST aged mice were infected with an AAV-Dlx-hM3Gq virus in the hilus of the DG and injected with CB21 to specifically activate the INs-SST. A behavioral battery tests was performed to evaluate the contextual and spatial memory. The stimulation of INs-SST improved spatial memory in aged mice. Also, the dendritic length and the synapses were analyzed by immufluorescence of specific synaptic markers. These results could help to develop novel therapeutic strategies to improve the formation of new memories and learning in conditions where neuronal plasticity is decreased.

Financing: Fodecyt Iniciación 11180777

Characterisation of habenular subpopulations in Corydora paleatus. A possible case of epithalamic symmetry.

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Left-right asymmetries of the brain are widespread in vertebrates and have been proposed to be essential for non-redundant neural processing. The epithalamus, comprising the habenulae and the pineal complex, is the most studied asymmetric neural structure in terms of morphology, development, and evolution. The habenulae is a bilateral neuronal relay complex connecting the forebrain and hindbrain, while the pineal complex is composed of the pineal organ and, in some species, the parapineal organ. In teleosts, the left and right habenular efferents segregate laterotopically in the interpeduncular nucleus (IPN), regardless of the large variability in the magnitude of habenular asymmetry within the group. According to developmental studies in the teleost zebrafish (Danio rerio), the most studied model of epithalamic asymmetry, the asymmetric distribution of the habenular cell populations is highly dependent on the presence of the embryonic parapineal organ. This evidence suggests that IPN laterotopy is associated with (and reveals) a left-right habenular patterning beyond its species-specific peculiarities. Here, we describe for the first time the habenula of Corydora paleatus, a teleost with a non-laterotopic IPN that could be a key counterexample model suitable to confirm this association. Using genetic markers and in situ hybridisation, we characterised the distribution of habenular subpopulations to exclude or confirm the presence of habenular symmetry. In addition, we used immunofluorescence to look for the presence of a parapineal organ due to its role in asymmetric habenular development. This study contributes to the understanding of the establishment and evolution of brain asymmetry and asymmetric neural circuitry.

Financing: Funding: ANID projects ACE 210007, ECOS-ANID C19B03 and FONDAP 15150012

Neuronal glutamate transporter EAAT3 regulates heterosynaptic GABAergic plasticity and reversal learning

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Long-term depression (LTD) is a form of synaptic plasticity that plays an important role in tasks involving the modification or elimination of previously learned information. Here we show that, presumably by regulating glutamate spillover between neighboring synapses, neuronal glutamate transporter (EAAT3) controls a form of heterosynaptic and endocannabinoid-dependent LTD at inhibitory synapses ("i-LTD") in the CA1 region of the hippocampus and contributes to the modulation of reversal learning. Using electrophysiological recordings in mouse brain acute slices, we demonstrate that overexpression of EAAT3 in principal cells does not alter the strength or short-term plasticity of excitatory synapses but significantly impairs i-LTD. Importantly, the i-LTD alteration was independent of endocannabinoid signaling modulation and mGluR functionality, was absent when EAAT3 was overexpressed at GABAergic interneurons, and can be rescued by pharmacologically blocking EAAT3 but not EAAT2 transporter, strongly suggesting that EAAT3 controls the escape of glutamate from excitatory synapses to neighboring GABAergic synapses to regulate i-LTD in the hippocampus. Behaviorally, using the Morris water maze, we found no detectable changes in the acquisition phase of spatial learning and memory process when EAAT3 was overexpressed in either principal cells or GABAergic interneurons. However, a marked impairment in reversal learning was observed only in mice overexpressing EAAT3 at principal cells, but no at GABAergic interneurons. Altogether our data support the notion that EAAT3 regulates the strength and the extent of receptor activation by afferent activity, and thus controls a form of heterosynaptic LTD at inhibitory synapses and contributes to regulate cognitive flexibility processes.

Financing: This work was supported by the Chilean government through FONDECYT Regular # 1201848 (AEC), # 1231012 (PRM). CAG was supported by a PhD fellowship #21201603 from ANID.

Computational identification of monocarboxylate transporter inhibitory molecules and their validation as targets for the treatment of glioblastoma

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Glioblastoma (GB) is the most prevalent, aggressive, and fatal form of cancer of the central nervous system, causing neurological issues such as seizures, memory loss, and speech and language defects. Currently, there is no cure for GB, and the average survival time for patients with this condition is 14.6 months.

This type of extremely malignant brain tumor has a high rate of lactate generation, which enables it to maintain its proliferation and the acidity of the tumor microenvironment. Lactate transport from the highly glycolytic center to the periphery of the GB is mediated by monocarboxylate transporters (MCTs), been MCT1 and MCT4 attractive therapeutic targets for the treatment of this pathology.

The lack of readily available three-dimensional structures for these transporters has hindered the development of MCT blocker molecules. This is especially important for MCT4, for which no selective inhibitors have been identified and little is known about the residues mediating its transport activity.

Using molecular docking and virtual screening strategies, we carried out a search for MCT1 and MCT4 inhibitory ligands, evaluating their activity first in HEK293 cells transfected with a FRET-type lactate sensor (Laconic) and then in a Drosophila melanogaster GB in vivo model.

We identified, piceatannol and NCI5, which were able to inhibit lactate transport by more than 50% in cells expressing only MCT1 or both transporters. In addition, treatment of GB flies with these ligands significantly decreased tumor volume and the number of GB-associated cells.

Developmental GABA ambient determine the cortical excitability profile in the FXS mice.

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Fragile X Syndrome (FXS) is a neurodevelopmental disorder and the most common cause of inherited intellectual disability and autism spectrum disorders. FXS etiology is determined by the loss of expression of Fragile X Mental Retardation Protein (FMRP). Multiple investigations have revealed a role for FMRP in shaping sensory circuit during development critical period to affect neurodevelopment. A cellular phenotype to this disruption is altered excitatory-inhibitory balance, resulting in a hyperexcitable neuronal network. In particular, the GABA inhibition system, which is a key contributor to the excitatory synaptic network maturation and excitability, is diminished in FXS. However, despite this evidence, not much is known about how extracellular levels of GABA and via what mechanisms these contributions take place during development in the hyperexcitable FXS phenotype. In this work we used a combination of molecular, electrophysiology and imaging approaches to test whether tonic GABAergic transmission correlates to the excitability network profile seen during development in the cortex of a murine model of FXS. We show that overall ambient GABA is diminished throughout development, and the developmental trajectory of GAD and GABA receptor subunits expression at the cortex is altered. These results seem to correlate with our measurements of tonic GABA transmissions and network excitability during early postnatal development of a Fmr1 KO mice model. These data suggest the important role of tonic GABA signaling in regulating network excitability during development and the implications, extending not only to developmental processes but also reverberating through the very phenotype of the syndrome.

Financing: DICYT 022001 CDR FONDECYT 1220680

Contribution of tau protein on the cognitive decline and mitochondrial impairment present during the aging

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Tau protein is critical in regulating microtubule stability, axonal transport, and synaptic function in the central nervous system. Current studies indicated that pathological modifications of tau have been associated with mitochondrial dysfunction, synaptic failure, and cognitive decline in Alzheimer´s disease (AD). Interestingly, synaptic impairment, oxidative damage, and mitochondrial failure are present during aging and could be responsible for cognitive and memory decline. We previously showed that genetic reduction of tau expression prevented hippocampal mitochondrial failure and improved cognitive performance compared to aging mice with endogenous tau expression. However, the mechanism by which tau contributes to these hippocampal abnormalities during aging is unknown. To test this hypothesis, we used C57BL/6 mice with 2-15-28-month-old to evaluate hippocampus-cognitive performance by behavioral tests (NOR and Barnes maze). Complementary, we evaluated mitochondrial function using fluorescence indicators, and mitochondrial/tau interactions were studied by western blot.

Additionally, to corroborate these findings, we use immortalized cortical neurons transfected with GFP, GFP-full-length-tau, and GFP-full-length-tau-OMP25 to direct tau expression into mitochondria and studied mitochondrial bioenergetics by live cell imaging. Behavioral tests revealed that 15- and 28-month-old mice significantly reduced cognitive and memory performance. Also, isolated hippocampal mitochondria showed a significant association of tau with mitochondria and an impaired bioenergetics function in aging mice. Notably, CN1.4 cells expressing GFP-T4-OMP25 reproduced these mitochondrial bioenergetics abnormalities shown in the hippocampus of aging mice. These results suggest that the pathological interaction between tau/mitochondria is present during aging, and this association may contribute to mitochondrial dysfunction, which is relevant to the cognitive loss present during aging.

Financing: ANID, FONDECYT 1200178 (RAQ) and Universidad Autónoma de Chile (MAO)

A murine model of sensorineural hearing loss in multiple sclerosis

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Sensorineural hearing loss (SNHL) is a prevalent sensorial impairment present in multiple sclerosis (MS) -the main CNS demyelinating disease. However, there is no agreement on the cellular mechanisms behind this dysfunction, nor on a putative value of SNHL as adiagnosis or prognosis tool for MS. Currently, there are no preclinical animal models to study the cellular mechanisms of this process. Here we propose to set a murine model that resembles the main characteristics of SNHL observed in MS. Data from literature suggest the brainstem (BS) as a putative target to induce SNHL by demyelination. We choose the inferior colliculus (IC) as an ideal target due to its key role in the integration and relay of sensory signals of the auditory pathway. We are setting an in vivo model of focal demyelination in the BS by injecting lysolecithin (LPC, a toxin that kills oligodendrocytes specifically) bilaterally in the IC. We are developing the histological characterization of demyelinated lesions in the target regions, identifying myelin content and cellular populations by immunofluorescence of specific markers, i.e. MBP for myelin, along with Olig2, GFAP and Iba1 for oligodendroglia, astrocytes and microglia, respectively. To assess the sensorineural readout of the model we are performing Auditory Brainstem Response (ABR) measurements to determine the auditory threshold and synchronous activation at 7, 14, 21, and 30 days post-LPC injection. Our preliminary results show that focal demyelination of the IC in our murine model resembles the SNHL characteristics observed in MS patients.

Financing: Funded by fondecyt 1210940 to F.C.O.

Acknowledgments: Mechanisms of Myelin Formation and Repair Laboratory, Departamento de Biología, Facultad de Química y Biología, Universidad de Santiago de Chile, Chile.Johns Hopkins School of Medicine, Otolaryngology Head and Neck Surgery Department

Effects of speech therapy on RMI-identified demyelinated lesions and cognitive-communicative skills in multiple sclerosis: a case report.

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Multiple Sclerosis (MS) is an autoimmune/neurodegenerative disease affecting central nervous system's (CNS) myelin. MS patients present an extensive CNS myelin loss (i.e. demyelinated lesions) leading to several neurological symptoms such as fatigue, locomotor dysfunction and cognitive-communicative skills declination. In experimental murine MS models, our group and others have demonstrated that preserving a neuronal activity in demyelinated axons promote myelin repair along with the consequent functional recovery of the animals. These pre-clinical studies allow for presuming that motor, cognitive or speech therapies designed to reinforce specific tasks (i.e. specific neural circuits), could reduce or at least slow down the progression of demyelination in MS patients, what should be reflected in a reduction of disease advance. To evaluate this premise, we developed a retrospective study by comparing the ranking values of six different tests normally used to evaluate MS progression (i.e. EDSS, BICAMS, MSQOL-54, Beck's depression inventory, MEC, and mini-SEA) along with magnetic resonance imaging (MRI) reports, of a MS patient before and after her/his speech therapy sessions (6 months during 2021). Importantly, MRI reports did not indicate any significant increment of demyelinated lesions in the examined period (2017 to 2023) while most of the MS progression tests did not show the expected detrimental progression for a 3 to 5 years period neither. Our results suggests that the speech therapy reduced -or at least slow down- MS progression in the patient, reinforcing the hypothesis that a preserved neuronal activity could promote the functional recovery in MS and other demyelinated diseases.

Financing: FONDECYT 1210940

Sexual differences in Nrf2-antioxidant pathway activation in a murine model of multiple sclerosis

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Multiple sclerosis (MS) is an irreversible progressive disease that affects women over men and is characterized by the loss of myelin, neuroinflammation, and an overproduction of reactive oxygen species (ROS), that have been linked to impairments of the Nrf2-signaling pathway. This antioxidant factor prevents mitochondrial failure, oxidative damage, and neuroinflammation. Additionally, it is known that TGFβ-1 is a major cytokine involved in the inflammatory response in MS. However, it is not clear whether TGFβ-1 dependent signaling could modulate Nrf2 activation, and if this alteration is different between males and females in MS. We studied the participation of TGFβ-1 in the activation of the Nrf2 pathway in an animal model of MS consisting of feeding mice with 0.25% cuprizone for 5 weeks and treated with a specific TGF-β Receptor 1 blocker (galunisertib). Nrf2 and TGFβ-1 expression was studied by immunofluorescence, RT-PCR, and western blot at 3 and 5 weeks in demyelinated lesions. Mitochondrial function was estimated by measuring ATP. Novel Object Recognition and Rotarod tests were made to study memory and physical condition. At 3 weeks, female animals showed a decrease in Nrf2 expression with an increase in ATP levels compared to males. At 5 weeks, a decrease in ATP levels and no changes in Nrf2 expression were observed. Memory and locomotor activity were different between male and female mice. These findings were modified with galunisertib treatment suggesting that demyelination-cuprizone induced could be affecting more female mice through impairment in the Nrf2 pathway and this could be dependent on TGFβ-1

Financing: FONDECYT 1210940 (FO); 1200178(RQ); INGE210017 (CG)

Acknowledgments: Laboratory of Neurodegenerative Diseases, Universidad Autónoma de Chile FONDECYT 1200178

Gaming expertise induces meso-scale brain plasticity and efficiency mechanisms as revealed by whole-brain modeling

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Video games have emerged as a valuable tool for studying the effects of training and neural plasticity on the brain. The opportunity presented by expertise in playing video games allows us to investigate the structural changes associated with gaming experiences and expertise. Here, we used a semi-empirical whole-brain model to propose structural neural plasticity mechanisms linked to video game expertise. We hypothesized that video game expertise is associated with neural plasticity-mediated alterations in structural connectivity that manifest at the meso-scale level, resulting in a more segregated functional network topology. To test this hypothesis, we combined structural connectivity data of StarCraft II video game players (VGPs) and non-players (NVGPs), with computational models. We employed graph theory analysis on simulated fMRI time series during resting-state conditions and under external stimulation. First, we observed that VGPs' functional connectivity is characterized by a meso-scale integration, with increased local connectivity in frontal, parietal and occipital brain regions. Regions that increased their connectivity strength in VGPs are known to be involved in cognitive processes crucial for task performance such as attention, reasoning, and inference. Furthermore in-silico stimulation indicated that differences in FC between VGPs' and NVGPs emerge in noisy contexts, specifically when the noise level was increased. This suggests that the connectomes of VGPs may facilitate the filtering of noise from stimuli. Overall, our work gives mechanistic insights about the consequences of structural neural plasticity triggered by video game experiences. These structural alterations drive the meso-scale functional changes observed in individuals with gamers' expertise.

Financing: CC-O was supported as Atlantic Fellow of the GBHI at Trinity College Dublin, and postdoctoral grant (BrainLat).AI is supported by ANID/FONDECYT-Regular (1210195;1210176;1220995); ANID/FONDAP/15150012; ANID/PIA/ANILLOS ACT210096; FONDEF ID20I10152; ANID/FONDAP 15150012; ReDLat PO by ANID/Fondecyt 1211750, AC3E/Basal FB0008.NK-G supported by the National Science Centre Grant: 2013/11/N/HS6/01335.

Acknowledgments: The authors are grateful to Blizzard Entertainment Inc. for their help, and to StarCraft II players and controls who kindly participated in the experiment.

Cortical regions and reversal learning: synchronization of neural circuits during sleep and its influence in behavioral performance

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Sleep is a physiological state that plays several fundamental roles in survival. Among these roles, sleep is critical for hippocampus (HC)-dependent memory formation, as it sustains synaptic plasticity through multiple coordinated cortical oscillations. Besides memory, the HC is also involved in generating abstract representations of the physical environment (spatial mapping), which are essential for spatial navigation. Anatomically, the HC has dense reciprocal projections with the prefrontal cortex (PFC) and the retrosplenial cortex (RSC). The PFC is involved in context-spatial decision-making, whereas the RSC is involved in transforming egocentric (self-centered) into allocentric (environment-centered) spatial navigation. Our objective is to determine the frequency band at which CA1v-PFC and CA1d-RSC circuits synchronize, the occurrence of such synchronization during a spatial navigation task and sleep, and to evaluate the influence of sleep on circuit synchrony and task performance. For this purpose, we train freely-moving rats to perform a spatial learning task based on allocentric navigation, recording their cerebral activity using 16 electrodes during task execution, followed by a sleep session. Preliminary results show that coherence between CA1d-RSC and CA1v-CA1d emerges in the theta frequency, but such frequency is slower during REM sleep than during the task. Also, information transmission in the theta band between CA1d-CA1v seems more prominent during REM than during task execution. Yet, during task execution, PFC-CA1v transmission occurs at various frequency ranges, each one related to specific stages through the task. These observations offer initial insights into the interplay of these brain regions during the execution of cognitive tasks and sleep.

Financing: Fondecyt N°1230589 Proyecto Anillo ACT210053

Does music-based therapy have effects on CNS cellular physiology? : a systematic review

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Key words: Music-based therapy, central nervous system & cellular physiology.

Summary: Music-based therapy (MB-ther) has een used by decades in a variety of conditions, including neurodegenerative di eases. It has been shown that MB-ther improves motor and cognitive impairment in both patients and rodent models. Although some reports rise possible cellular mechanisms underlying the phenomena (i.e. changes in neurotransmitter levels), there is no systematic studies showing the actual effect of MB-ther on central nervous system (CNS) cellular physiology. We wondered whether the scientific literature supports the hypothesis: "MB-ther modifies CNS cellular physiology". To this end we performed a systematic review considering articles published from 1980 to 2023 in both PubMed and ScienceDirect databases under the search "music based therapy" + "brain cell"/"neuron"/"glial cell"/"cell physiology"/"neurodegenerative disease". We only considered articles stating clearly the characteristics of the stimuli and the studied CNS area and cellular type. 151 articles from PubMed plus 32 articles from Sc enceDirect met these initial criteria. Then, we defined an "effect on cell physiology" as any reported change on (i) cell metabolism, (ii) cell excitability and/or (ii) secretory activity of cells. Under these (general) restrictions only 19 articles (out of 183) can be considered as investigations proving an effect of MB-ther on CNS brain cells physiology. Thus, in our hands only ~ 10 % of the reviewed articles support an effect of MB-ther on CNS cells physiology (under our definition). Our results evidence the necessity of further studies to determine the cellular mechanisms underlying the reported effects of music-based therapies on neurodegenerative diseasepatients (i.e. motor and cognitive improvements)

Acknowledgments: Mechanisms of Myelin Formation and Repair Laboratory, Departamento de Biología,Facultad de Química y Biología, Universidad de Santiago de Chile,

The activation of TASK-1/TASK-3 channels by JG-C3-98 reduces thermal and mechanical sensitivity of primary somatosensory neurons.

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K2P channels underlie background K^+ currents that stabilize the resting membrane potential of excitable and non-excitable cells. As such, their activation hyperpolarizes the membrane potential, acting as molecular excitability brakes of neuronal activity. In the somatosensory system, the K2P channels TASK-1 and TASK-3 have a relevant role in cold sensing, mechanosensitivity, and pain. Combining Ca^{2+}-imaging in cultured primary sensory neurons, extracellular recording of the nerve endings of trigeminal ganglia (TG) neurons at the corneal surface, and behavioral analysis, we studied the effect of the novel and rationally designed activator of TASK-1/TASK-3 channels JG-C3-98 on thermal and mechanical sensitivity. We have found that the activation of TASK-1/TASK-3 channels using JG-C3-98 shifted the thermal threshold of cold thermoreceptor neurons in culture ~2°C to lower temperatures. Aditionally, in cultured TG neurons responding to hypoosmotic stimulation, the activation of TASK-1/TASK-3 channels also reduced their maximal mechanically evoked responses. In corneal cold-sensitive neurons recorded ex vivo, JG-C3-98 also shifted the thermal threshold of the nerve endings to lower temperatures. Moreover, the activation of TASK-1/TASK-3 channels in vivo by local administration of JG-C3-98 in the hind paw reduces the mechanical sensitivity and AITC-evoked nociceptive responses in mice. These results suggest that JG-C3-98 could be considered as a potentially effective pharmacological tool to simultaneously

reduce thermal and mechanical sensitivity at different somatosensory territories in physiological and pathophysiological conditions.

Financing: Supported by Millennium Nucleus of Ion Channel-Associated Diseases (MiNICAD) (WG, RM, MP), FONDECYT 1230446 (WG), DICYT-VRIIC 022143PP (MP), VRIIC-USACH 021843MM (RM), and Millennium Nucleus for the Study of Pain (MiNuSPain) (RM, MP).

Validation of Chromatic Pupillometry as a Biomarker for Early Diagnosis of Chronic Open-Angle Glaucoma

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Background: Glaucoma, the leading cause of irreversible blindness worldwide, affects approximately 3.4% of the global population, with a national prevalence of around 2%. Its progressive and irreversible nature, driven by the gradual loss of retinal ganglion cells (RGCs), underscores its complexity. Asymptomatic vision loss complicates early detection, delaying timely intervention. The lack of effective strategies for early-stage patient identification necessitates innovative approaches. Intrinsically photosensitive retinal ganglion cells (ipRGCs), comprising only 1% of RGCs and responsive to 480 nm wavelengths due to melanopsin expression, offer a unique avenue. Chromatic pupillometry leverages the pupillary reflex tied to ipRGCs' non-visual functions. We hypothesize that alterations in pupillary response to short-wavelength light stimuli could signify early glaucoma stages.

Methods: Our study classified participants into two groups (glaucoma patients and healthy controls). Each participant was exposed to a randomized sequence of light stimuli, including 1-second flashes or 1-minute ramps, at different wavelengths (480 nm blue, 520 nm green, 600 nm red, and white), with one-minute rest intervals interspersed. The pupillary response was recorded using a pupillary and eye movement recording device that was integrated with an LED illumination system.

Results: Preliminary findings demonstrate distorted pupillary responses to light stimuli in glaucoma patients, highlighting the potential for an early deterioration indicator with diagnostic significance.

Conclusion: This study pioneers diagnostic techniques, enabling early therapeutic interventions to mitigate glaucoma›s progression and associated impairments. The proposed biomarker, facilitated by chromatic pupillometry, holds promise in revolutionizing glaucoma diagnosis and management.

Keywords: Biomarkers; Glaucoma; Intrinsically photosensitive retinal ganglion cells; Pupillary response.

Financing: Department of Medical Technology Competitive Research Fund. DETEM 2022 - 570372

Acknowledgments: Fondo Concursable de Investigación DETEM 2022 – 570372; Iniciativa Científica Milenio ICN09_015 Proyecto ACE 210007.

Classification of EEG Signals and Auditory Recordings from a Visual/Auditory Attention Task in Tinnitus Patients

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Chronic non-pulsatile tinnitus (CNPT) is a condition characterized by the perception of sound in absence of corresponding external stimuli. Since it is a model of abnormal perception, markers have been primarily sought at brain level. However, taking into consideration the efferent auditory system allows for measurements that provide physiological information about the integrity of the auditory pathway, in this case, through the continuous recording of otoacoustic emissions (OAEs). In the current investigation, a task of visual/auditory selective attention was performed (Dragicevic, 2019) on 14 CNPT/14 healthy subjects. OAEs were simultaneously recorded along with brain activity through a 32-channel EEG. We aimed to classify the signals in two domains to determine if a single trial: 1. Corresponded to visual or auditory attention; 2. Belongs to a CNPT patient. For the classification between attentional states, accuracy was around 80% when using both sources and close to 75% with EEG. In CNPT/Healthy classification, EEG channels and both combined sources provided values close to 90%. In both procedures, the use of microphonic channel resulted in correct classifications in 60-70% of cases. Additionally, we determined the most discriminant EEG channels to provide greater physiological interpretability to our results. We concluded, the inclusion of the OAEs enhances classification for attentional states but not for CNPT/Healthy classification. This suggests that the biomarkers of CNPT are predominantly located at the brain level. However, virtual cochlear channels were derived from a single microphone recording, the inclusion of additional sources of the same nature could potentially enhance the results.

Financing: Funded by Proyecto Fondecyt 1220607, CONICYT BASAL FB008 and Programa ANID Becas de Doctorado Nacional.

Development and maintenance of the columnary organized visual DVR: retinal input is not necessary.

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The dorsal ventricular ridge (DVR) is the main structure within the avian pallium that contains terminal regions for ascending sensory pathways. In precocial birds, the sensory pathways are established precisely during embryonic development. In particular, the visual DVR (vDVR) exhibits an organized columnar, topographic, homotopic connectivity between its thalamic recipient territory (entopallium, E) and its associative region (mesopallium, M), which is established early in development and independent of early retinal input. However, it is yet to be determined if the retinal afferences sustain the overall organization of this neuronal arrangement at late embryonic and postnatal stages. To assess this, we performed "in-vivo" mechanical mono and bi-enucleations in precocial chick embryos at 14 days of incubation (E14), to subsequently evaluate the neuroarchitecture and neurochemical features of the visual pallium. Interestingly, in spite of the significant effect in sub-telencephalic targets: the mesencephalic optic tectum (TeO) loses precise stratification and thickness and the thalamic nucleus rotundus (Rt) decreases in volume, the highly organized Rt-vDVR projection and the reciprocal, topographic connections within the vDVR were unaffected by enucleations. Combined with previous findings, these results suggest that the organization at higher stages of this visual pathway in a precocial bird is not influenced, at early or late stages, by retinal activity. In particular, retinal afferents seem not to be necessary for the initial establishment and late maintenance of the overall organization of the vDVR.

Financing: PROYECTO FONDECYT 1210069

Higher functional connectivity between supramammillary nucleus and hippocampus during active exploration behaviors

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Hippocampal theta rhythm is a field potential oscillation between 6-12 Hz present along different stages of the sleep-wake cycle. Its physiological role is thought to support a wealth of cognitive functions such as memory and spatial exploration. Hippocampus itself is known for being a theta generator, but there are several other brain regions capable of generating theta oscillations. Moreover, many of these regions send projections to the hippocampus, thus influencing its own theta rhythm generation. Among these regions, it's been shown that supramammillary nucleus regulates hippocampal theta oscillations during sleep-wake cycle. To shed light upon the functional and temporal relationships between the supramammillary nucleus activity and hippocampal theta oscillations we performed in-vivo electrophysiology experiments to record field potentials in freely moving rats. We show that supramammillary nucleus increases its theta spectral power during active exploration instances, in contrast to REM sleep or quiet wakefulness (4 animals did 29 sessions, p= 0.0011307). Furthermore, this higher theta power is accompanied by an increase in the coherence between the supramammillary nucleus and hippocampal areas dentate gyrus and CA1 (p= 6.23924e-11 for dentate gyrus and 6.26612e-9 for CA1). These results suggest that the coupling between the supramammillary nucleus and the hippocampus increases during active wakefulness.

Financing: FONDECYT 1230589

A causal role for the parietal cortex in ambiguity computations in humans

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Humans often face the challenge of making decisions between ambiguous options. The level of ambiguity in decision-making has been linked to activity in the parietal cortex, but its exact computational role still needs to be discovered. To test the hypothesis that the parietal cortex plays a causal role in computing ambiguous probabilities, we conducted consecutive fMRI and TMS-EEG studies where 64 participants made decisions in ambiguity and no-ambiguity conditions. Using computational cognitive modeling in behavioral data, we found that participants assigned unknown probabilities to objective probabilities, elevating the uncertainty of their decisions. Using fMRI, we found that Parietal cortex activity correlated with both the objective degree of ambiguity and a process that underestimates the uncertainty during decision-making. Conversely, the midcingulate cortex encodes prediction errors and increases its connectivity with the parietal cortex during outcome processing. Disruption of the parietal activity by TMS stimulation increased the uncertainty evaluation of the options, decreasing cingulate cortex oscillations during outcome evaluation. These results provide evidence for a causal role of the parietal cortex in computing uncertainty during ambiguous decisions made by humans.

Financing: This work was supported by Agencia Nacional de Investigación y Desarrollo de Chile (ANID), FONDECYT (1181295 and 1211227 to P.B.), PAI (PAI77190047 to P.S-I), ECOS/CONICYT (C12S03), FONDEQUIP EQM150076.

Acknowledgments: We want to thank Leonie Kausel and Anne Bliss for proofreading the manuscript

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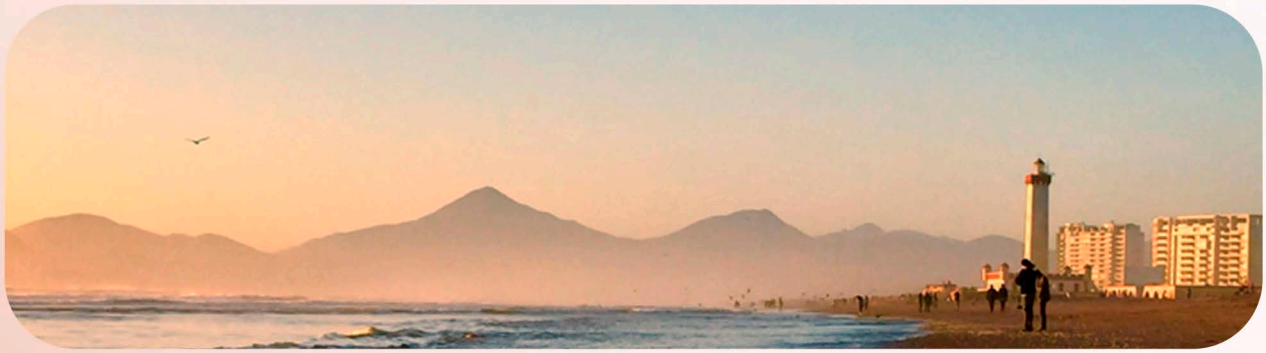

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