Sociedad Chilena de Neurociencia

XVI ANNUAL MEETING SOCIEDAD CHILENA DE NEUROCIENCIA

November 10-12, 2020

ABSTRACTS BOOK

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XVI Annual Meeting of the Chilean Society for Neuroscience

10 to 12 November 2020

Virtual Annual Meeting

MESSAGE FROM THE PRESIDENT

Mensaje de Bienvenida

Bienvenidos a la XVI Reunión Anual de la Sociedad Chilena de Neurociencias. En primer lugar, deseamos que todos y todas estén sanos y bien. Como todos saben durante este año correspondía la reunión de FALAN programada para septiembre 2020 en Belén, Brasil. Sin embargo, estamos enfrentando los devastadores efectos asociados a la pandemia COVID19; y nuestra reunión internacional al igual que cientos de otras reuniones en el mundo fue cancelada.

Somos conscientes que durante todo el año 2020, nuestros socios y socias han debido enfrentar situaciones nuevas, algunas de ellas muy complejas. Sin embargo, tras la cancelación de la reunión internacional en Brasil, como directorio tomamos la decisión de preguntar a nuestros socios si querían tener una reunión virtual. Una abrumadora mayoría indico estar dispuesta a participar en una reunión remota. Por lo tanto, en primer lugar, queremos agradecer la voluntad de participar en este nuevo formato de reunión, que, si bien no nos permitirá establecer una comunicación como la que teníamos acostumbrada a tener en nuestras reuniones, servirá para que podamos volver a encontrarnos.

Una de las motivaciones principales para organizar una reunión remota, en un tiempo muy reducido, es que somos conscientes que ahora mas que nunca se hace necesario mantener algunos aspectos de la actividad científica que tanto nos apasiona. Con la gran mayoría de los laboratorios de investigación cerrados por meses, creemos fundamental proveer un espacio de discusión que sirva a los neurocientíficos del país sin importar el estadio de la carrera científica en que estén. Y es por esto por lo que tomamos la decisión que el registro para los estudiantes de pre y postgrado fuera sin costo.

Nuestra reunión tiene mas de 400 inscritos, y durante sus tres días presentará 8 simposios, con 29 connotados invitados nacionales e internacionales, 2 conferencias plenarias, 12 comunicaciones libres , más de 70 posters y 1 mesa redonda. Quisiera detenerme un momento en esta última actividad que abordará los efectos de la pandemia COVID sobre el cerebro. El confinamiento y las restricciones impuestas por la pandemia se prevé que tienen y tendrán un impacto enorme sobre los chilenos; y en este contexto hemos invitado a expertos que compartirán en una sesión abierta al publico general los diferentes efectos que ya se han observado y algunos que se esperan para nuestro país una vez liberados del confinamiento. Esta actividad creemos que es una señal concreta sobre como nuestra Sociedad puede contribuir a informar y entregar opiniones expertas en ámbitos que son de gran relevancia para Chile.

Otro aspecto que quisiera señalar es que para la presente reunión hemos trabajado fuertemente en estimular la participación de investigadoras en nuestras actividades. Es así como la mitad de los expositores en simposio, así como las dos conferencias plenarias serán presentadas por investigadoras. De esta forma queremos avanzar decididamente en potenciar la visibilidad y generar los espacios que justamente nuestras investigadoras deben tener.

La posibilidad de ofrecer registro sin costo para los estudiantes de pre-y postgrado no habría sido posible sin la generosa contribución económica de nuestros auspiciadores, quienes en tiempos difíciles para ellos también, no han dudado en participar y apoyar nuestra reunión virtual. Agradecemos a la Fundación Guillermo Puelma, Galénica, GeneXpress, Loncotec y PrionLab. Les invitamos a visitar los stands virtuales e interactuar con los representantes de las empresas. También agradecemos la desinteresada contribución de los centros de investigación CINV, BNI y GERO.

Finalmente, quisiera públicamente agradecer a la directiva de la Sociedad Chilena de Neurociencias, a 4ID y a Yolanda Zambrano quienes no dudaron ni un segundo, y han trabajado fuerte y desinteresadamente para que esta reunión pueda ocurrir.

Invito a todos a disfrutar de estos 3 días de simposios, conferencias, comunicaciones libres y posters. Que la imposibilidad de vernos en persona no mine nuestro entusiasmo y compromiso por hacer crecer las neurociencias en el país.

Dr. Christian González-Billault
President
Sociedad Chilena de Neurociencia

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Congress Program

	November, Tuesday 10	November, Wednesday 11	November, Thursday 12
09:00 11:00	SYMPOSIUM 1	SYMPOSIUM 4	SYMPOSIUM 6 SYMPOSIUM 7
11:15 13:15	SYMPOSIUM 2 SYMPOSIUM 3	SYMPOSIUM 5	SYMPOSIUM 8
15:00 17:00	POSTER SESSION 1	ORAL COMMUNICATIONS 1, 2	POSTER SESSION 2
18:00 19:00	OPENING CONFERENCE Cecilia Flores	ROUNDTABLE CEREBROS EN PANDEMIA	CLOSING CONFERENCE Li-Huei Tsai

SYMPOSIUM 1

Cellular and Molecular Aspects of Neurodegenerative Pathologies.

Coordinator: **Andrea Paula-Lima**

Palmitate associates obesity to Alzheimer's disease.
Fernanda de Felice, Department of Neuroscience, Weston Brain Institute, Queen´s University, Toronto, ON, Canada.
Redox modifications and calcium-dependent synaptic proteins in the pathogenesis of Alzheimer's disease.
Andrea Paula-Lima, Department of Neuroscience, Faculty of Medicine and Institute for Research in Dental Sciences, Faculty of Dentistry, University of Chile.
Parkinson's disease: the mitochondria-iron link.
Marco T. Nunez, Department of Biology, Faculty of Sciences, Universidad de Chile.
Nutrient sensing and redox balance: GCN2 as a new integrator in aging.
Soledad Matus, Fundación Ciencia Para la Vida.

SYMPOSIUM 2

Closing the Circuit: From sensory stimuli to behavioral responses.

Coordinators: **Andrea Calixto, Chiayu Chiu and Karen Castillo**

PV neurons are sensitive to brief visual deprivation throughout life
Sandra Kuhlman, Department of Biological Sciences and Carnegie Mellon Neuroscience Institute, Carnegie Mellon University Pittsburgh, Pennsylvania.
Modulation of sensory ion channels by fatty acids.
Valeria Vazquez, The University of Tennessee, Health Science Center, Department of Physiology, Memphis, TN.
Olfactory dysfunction in a prodromal Parkinson's disease model: making every sniff count.
Gabriela Mercado, Translational Parkinson's Disease Research Laboratory, Center for Neurodegenerative Sciences, Van Andel Research Institute, Michigan.
Sensory neurons regulate C. elegans locomotion quiescence through GRK-2 signaling.
Irini Topalidou, University of Washington, Department of Biochemistry, Seattle, WA, Washington.

SYMPOSIUM 3

Neuroscience networking and multicentric approaches to dementia research in Latin America.

Coordinator: **Agustin Ibañez**

A Neurodegenerative Disease Landscape of Rare Mutations in Colombia Due to Founder Effects.
Kenneth S. Kosik, M.A, M.D.Harriman Distinguished Professor of Neuroscience, Neuroscience Research Institute, Dept of Molecular, Cellular, Developmental Biology, University of California, Santa Barbara, USA.
A method to prevent AD: Read and learn from Nature.
Francisco Lopera, Grupo de Neurociencias de Antioquia, Universidad de Antioquia, API, Colombia.
The Latin American Research consortium on the Genetics of Parkinson's Disease (LARGE-PD)
Ignacio Mata, Cleveland Clinic, US.
Genetics of Alzheimer's Disease in Latin America. Recent Advances and Future studies.
Jorge J Llibre-Guerra, Dominantly Inherited Alzheimer's Network Trials Unit; Knight Alzheimer's Disease Research Center; Department of Neurology, Washington University in St Louis, US.
A new framework for naturalistic speech assessment based on machine learning.
Adolfo Garcia, Cognitive Neuroscience Center (CNC), Universidad de San Andrés, Argentina; Atlantic Fellow, Global Brain Health Institute (GBHI) US.

SYMPOSIUM 4

Exploring key molecular determinants in pain neurophysiology.

Coordinators: **Rodolfo Madrid, Elias Utreras**

Role of Kv1.6 channel in blocking hyperexcitability after nerve injury.
Margarita Calvo, P. Universidad Católica de Chile.
Regulation of the polymodal thermo-TRP channel TRPM8 function by phosphorylation.
María Pertusa, Universidad de Santiago de Chile.
Glycine receptor modulation in chronic pain.
Gonzalo Yévenes, Universidad de Concepción.
Regulation of the P2X2 receptor channel by calcium and phosphorylation and its potential role on pain signaling.
Claudio Coddou, Universidad Católica del Norte.

SYMPOSIUM 5

Young Neuroscientist Symposium.

Coordinator: **Patricio Orio**

Breaking models: Optogenetic activation of the inhibitory nigro-collicular pathway evokes paradoxical contralateral orienting movement in mice.
Claudio Villalobos, University of California Los Angeles.
Nicotinic receptor triggered exocytosis in chromaffin cells requires activation of P2X7 receptors by an autocrine ATP mediated mechanism.
María Constanza Maldifassi, Universidad de Valparaíso, Universidad de Santiago de Chile.
Palmitic Acid Inhibits Autophagic Flux and Ciliogenesis Impairing Insulin Signaling in Hypothalamic Neurons.
Yenniffer Ávalos, Universidad de Santiago de Chile. Pontificia Universidad Católica de Chile.
Mab21l2 links morphogenesis and differentiation in developing zebrafish eyes.
Leonardo E. Valdivia, Universidad Mayor, Université de Toulouse, University College London.

SYMPOSIUM 6

Current Topics on Language Neural Processing.

Coordinators: **Rocio Loyola-Navarro and Ana Campos Espinoza.**

Natural language syntax, active inference and the hidden states of the world.
Elliot Murphy, Vivian L. Smith Department of Neurosurgery, University of Texas Health. Science Center.
Brain structures and brain rhythms relevant to language.
Marcela Peña, "acquisition". Facultad de Ciencias Sociales, Pontificia Universidad Católica de Chile.
Neural correlates of word learning in bilingual speaker.
Roberto A Ferreira, Facultad de Educación, Pontificia Universidad Católica de Chile.
Lateralization during language recovery post stroke and due to a brain tumor.
Carolina Mendez, Pontificia Universidad Católica de Chile.

SYMPOSIUM 7

Recent experimental designs to discover effective therapies to treat epilepsy.

Coordinator: **Juan Carlos Saez**

Cytokine-induced uncoupling of astrocytes as a cause of temporal lobe epilepsy.
Christian Steinhäuser, Institute of Cellular Neurosciences, University of Bonn. Bonn-Germany.
c-Abl signaling in Epilepsy damage: Projections for drugs searching.
Alejandra Alvarez, Department of Cell and Molecular Biology. Pontificia Universidad Católica de Chile.
Distinct contributions of neuronal and astrocyte pannexin1 to seizures.
Eliana Scemes, Department of Cell Biology and Anatomy, New York Medical College. New York, USA.
Inhibition of connexin hemichannels drastically mitigates epilepsy induced by inhibition of GABAA receptors.
Juan C. Sáez, Instituto de Neurociencias, Centro Interdisciplinario de Neurociencias de Valparaíso. Universidad de Valparaíso. Chile.

SYMPOSIUM 8

A Round Trip to Metabolism and Cognition.

Coordinator: **Jimena Sierralta**

Is behavior a consequence of the energetic hemostasis of neural circuits?.
Pedro Maldonado, Department of Neuroscience, Faculty of Medicine, Universidad de Chile and Biomedical Neuroscience Institute.
A trade-off between metabolic efficiency and predictive power in neural codes.
Abel Wajnerman, Department of Philosophy, Universidad Alberto Hurtado.
Perfect homeostasis: on the verge of death 4 times per second, for 100 years.
Felipe Barros, Centro de Estudios Científicos, Valdivia.
Cellular and functional aspects of energy transfer in brain cells.
Jimena Sierralta, Department of Neuroscience, Faculty of Medicine, Universidad de Chile and Biomedical Neuroscience Institute.

CONFERENCES

Opening Conference
How do experiences in adolescence shape the developing brain?.

Cecilia Flores Douglas Mental Health University Institute, de McGill University.
Coordinator: **Pablo Henny**

Closing Conference
Network level approaches to studying Alzheimer's disease.

Li-Huei Tsai, The Picower Institute, MIT, USA.
Coordinator: **Christian González**

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ROUNDTABLE

"Cerebros en Pandemia"

Coordinator: **José L Valdés**

Consuelo Aldunate Castillo, (Psiquiatria Infantil y de la Adolescencia), Departamento de Psiquiatría y Salud Mental Norte. Facultad de Medicina. Departamento de Neurociencias, Universidad de Chile.

Carlos Ibañez Piña, (Psiquiatra). Jefe de unidad de adicciones, Clínica Psiquiátrica Universitaria, Universidad de Chile. Departamento de Psiquiatría y Salud Mental Norte, Departamento de Neurociencias, Universidad de Chile

Juan Pablo Jiménez, (Psiquiatra), Departamento de Psiquiatría y Salud Mental Oriente, Facultad de Medicina. Director del Instituto Milenio para la Investigación en Depresión y Personalidad (MIDAP).

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CONFERENCES

How do experiences in adolescence shape the developing brain?

Cecilia Flores[1].
(1) Douglas Research Centre, Department of Psychiatry, McGill University

Adolescence is an age of increased vulnerability to mental illness, but we still know very little about the cellular and molecular process ongoing during adolescent brain development and how they are impacted by experience, including drugs of abuse and stressors. This talk focuses on the emerging role of axonal guidance cues in the maturation of the prefrontal cortex in adolescence and its implications for psychiatric susceptibility and resilience. I will discuss findings from rodent and human studies showing that risk and protective factors target guidance cue systems in adolescence, altering the organization of prefrontal cortex connectivity and cognitive function in adulthood. I will emphasize that the direction, magnitude, and enduring consequences of these effects vary between males and females and depend on the specific adolescent period.

Uncovering the role of Alzheimer's disease risk genes using stem cells and human brains

Li-Huei Tsai[1].
(1) The Picower Institute, MIT, USA

Alzheimer's disease (AD) is a debilitating brain disorder, with staggering human and financial cost. While genomic studies increasingly identify genetic risk alleles that correlate with AD, there is still no clear picture of the underlying molecular and cellular mechanism(s). My lab uses a multi-prone approach to understand how cellular, molecular and brain circuit dysfunctions contribute to AD. We recently reported the first single-cell transcriptomic analysis of the prefrontal cortex to decipher the cell types and molecular pathways impacted by AD (Mathys et al. 2019, Nature). In addition to known AD affected pathways, we found prominent alteration of oligodendrocyte lineage cells, broad cell type specificity of gene expression alterations, and association of pathology with cell-type specific up- or down-regulation. Moreover, we found that cells from female brains are over-represented in disease-associated subpopulations and that transcriptional responses were substantially different between sexes in several cell types including oligodendrocytes. Together, these observations highlighted the power and utility of single-cell resolution studies for brain disease research. This has motivated us to expand our single-cell investigation of AD, including additional brain regions and risk genotypic backgrounds.

To validate the new hypotheses generated from single cell-level analysis, we used patient derived induced pluripotent stem cells (iPSCs) to model disease risk genes and pathology. Using human iPSC-derived astrocytes, brain endothelial cells and pericytes, we recreate the human blood brain barrier in vitro (iBBB), creating a highly tractable model that recapitulates key anatomical and physiological properties of the BBB. Using isogenic ApoE3 and ApoE4 iPSC lines to generate iBBBs, we find amyloid accumulation on the iBBB, and that APOE4 iBBBs exhibit significantly more amyloid accumulation than APOE3 iBBBs. Through combinatorial experiments, we pinpoint the causal cells through which APOE4 predisposes cerebral amyloid angiopathy (CAA), a condition seen in a large proportion of AD patients. We identify the pathways underlying the accumulation of amyloid along the iBBB and find that inhibiting these pathways with FDA-approved drugs prevent the build-up of amyloid in APOE4 iBBBs. We are currently leveraging the isogenic ApoE iPSC lines, and human single cell transcriptomic data to investigate how ApoE4 impacts other brain cell types to predispose the development of AD pathology and symptoms.

SYMPOSIUM

SYMPOSIUM 1

Cellular and Molecular Aspects of Neurodegenerative Pathologies.

Coordinator: Andrea Paula-Lima

Palmitate Associates Obesity To Cognitive Impairment

Fernanda De Felice[1].
(1) Without Affiliation

Obesity has been associated with cognitive decline, atrophy of brain regions related to learning and memory, and higher risk of developing dementia. By using a combination of behavioral characterization with biochemical, molecular, and electrophysiological techniques, Dr. DeFelice has obtained a vertically integrated perspective on Alzheimer´s disease neurobiology, from the molecular to the cognitive level. Dr. DeFelice, a Brazilian researcher, is now interested in identifying mechanisms underlying obesity-related memory impairment, with the aim to test treatments to alleviate memory deficits. Her group recently reported the effects on the brain of palmitate, a saturated fatty acid present in high amounts in fat-rich diets. They found that palmitate is increased in the cerebrospinal fluid (CSF) of overweight and obese patients with amnestic mild cognitive impairment. Also, they showed that in mice, intracerebroventricular infusion of palmitate impairs synaptic plasticity and memory. Moreover, palmitate was shown to induce astroglial and microglial activation in the mouse hippocampus, and its deleterious impact is mediated by microglia-derived tumor necrosis factor alpha (TNF-a) signaling. Therefore, their results establish that obesity is associated with increases in CSF palmitate and activation of a pro-inflammatory mechanism. Collectively, Dr. DeFelice´s contributions suggest a mechanism by which excess palmitate derived from unhealthy diets affects brain function and contributes to cognitive impairment in patients with obesity.

Redox Modifications And Calcium-Dependent Synaptic Proteins In The Pathogenesis Of Alzheimer's Disease. (Modificationes Redox En Proteinas Sinápticas Dependientes De Calcio En La Patogénesis De La Enfermedad De Alzheimer)

Andrea Paula-Lima[1,2,3], Pedro Lobos[3], Tatiana Adasme[5], Cecilia Hidalgo[1,3,4].
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(2) Universidad de Chile, Institute for Research in Dental Sciences, Faculty of Dentistry, Sergio Livingstone Pohlhammer, 943, Santiago, Chile
(3) Universidad de Chile, Biomedical Neuroscience Institute, Faculty of Medicine, Independencia 1027, Santiago, Chile
(4) Universidad de Chile, Institute of Biomedical Sciences, Faculty of Medicine, Independencia 1027, Santiago, Chile
(5) Universidad Bernardo O´Higgins, Centro Integrativo de Biología y Química Aplicada, Centro, Viel 1497, Santiago, Chile

Oxidant species and calcium jointly contribute to the synaptic plasticity defects induced by amyloid-β peptide oligomers (AβOs), the distinctive synaptotoxic markers of Alzheimer's disease. We have reported that AβOs elicit abnormally long-lasting Ca2+ signals, arising from the joint activation by Ca2+ and ROS of ryanodine receptor (RyR) channels, which act as Ca2+-sensitive cellular redox sensors. AβOs injections directly into the hippocampus, by engaging oxidation-mediated reversible pathways, significantly impair spatial memory, decrease hippocampal glutathione levels and overall content of plasticity-related proteins (c-Fos, Arc, and RyR2). We also have recently reported that N-acetylcysteine-fed rats subsequently injected with AβOs displayed the same behavior in the spatial memory task as control rats, highlighting the use of strategies based on antioxidant therapy to counteract the harmful effects of AβOs on hippocampal synapses. Here we will discuss how redox modifications in synaptic components can be considered as biomarkers of cognitive status, in brain aging and disease.

ICN09_015; BMBF180051
Ryanodine receptors, Memory, Antioxidants

Parkinson's Disease: The Mitochondria-Iron Link

Marco Tulio Nuñez[1], Bruce K. Cassels[2], Alejandro Roth[1], Pabla Aguirre[1], Victoria Tapia[1], Olimpo García-Beltrán[3]
(1) Universidad de Chile, Biology, Faculty of Sciences, Las Palmeras 3425, Santiago, Chile
(2) Universidad de Chile, Chemistry, Sciences, Las Palmeras 3425, Santiago, Chile
(3) Universidad de Ibague, Faculty of Natural Sciences and Mathematics, Ibagué, Colombia

Neurons depend on optimal mitochondrion function to support their myriad of functions, including the maintenance of ionic gradients. A common feature of a number of neurodegenerative diseases, including Alzheimer's Disease and Parkinson's Disease (PD), is mitochondrial dysfunction. Mitochondria not only have a key role in electron transport and oxidative phosphorylation. Their dysfunction is associated with decreased ATP levels, decreased glutathione levels, increased oxidative damage and calcium, iron and protein dyshomeostasis.Mitochondrial dysfunction and oxidative stress have long been implied as one of the pathophysiological mechanisms underlying PD. Mitochondria isolated from human brain tissues and peripheral cells of sporadic PD patients exhibit reduced mitochondrial complex I activity, and postmortem substantia nigra tissue from idiopathic PD patients display a decreased number of complex I subunits. We have proposed a model in which mitochondria dysfunction is an early pathological alteration in PD neuronal death. In this context, we have impulsed a therapeutic strategy with the use of multi-target mitochondriotropic compounds with properties that attack multiple symptoms of the neurodegenerative process, namely free radical neutralizing activity, iron chelating activity, selectivity for dopaminergic neurons and inhibition of monoamine oxidase B (MAO-B). In this symposium we will present evidence obtained from cell and animal model of the disease that validates the use of multifunctional coumarins for the treatment of PD.

Financed by FONDEF project 17I10095 from ANID.
Parkinson, mitochondria, multitarget drugs

Role Of The Integrated Stress Response In Neurodegeneration.

Soledad Matus[1,2,3], Nicolas Martinez[1,2], Luis Osorio[1], Felipe Gomez[1]
(1) Fundación Ciencia & Vida, Zañartu 1482, Ñuñoa, Santiago, Chile
(2) Universidad San Sebastian, Carmen Sylva 2444, Santiago, Chile
(3) Biomedical Neuroscience Institute,, Faculty of Medicine, Independencia 1027, Santiago, Chile

In response to diverse stress stimuli, including nutrient restriction, infections, or proteotoxicity, eukaryotic cells activate a common adaptive pathway, termed the integrated stress response (ISR), to restore cellular homeostasis. Dr. Matus has focused on understanding the contribution of this signaling pathway to the neurodegenerative process and aging. Using in vivo and in vitro models, she has studied the consequences of targeting ISR components to open new therapeutic strategies for treating neurodegenerative diseases. She has recently studied the consequences of ISR activation in neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and Alzheimer's diseases (AD). She will discuss the role of ISR mediated protein synthesis inhibition in ALS progression and stress sensors as drivers of the neurodegenerative process observed in AD.

This work was supported by "Programa de Apoyo a Centros con Financiamiento Basal" AFB-170004 (to Fundacion Ciencia & Vida), FONDAP program 15150012, Millennium Institute P09-015-F FONDECYT, and Postdoctoral Fellowship 3200932

Integrated Stress Response, Neurodegeneration, ALS

SYMPOSIUM 2

Closing the Circuit: From sensory stimuli to behavioral responses.

Coordinator: Andrea Calixto, Chiayu Chiu and Karen Castillo

PV neurons are sensitive to brief visual deprivation throughout life

Sandra Kuhlman[1].
(1) Carnegie Mellon University, Biological Sciences, 4400 Fifth ave, Pittsburgh, United States

Activity of cortical inhibitory interneurons is rapidly reduced in response to monocular deprivation during the critical period for ocular dominance plasticity and in response to salient events encountered during learning. In the case of primary sensory cortex, a decrease in mean evoked firing rate of parvalbumin-positive (PV) inhibitory neurons is causally linked to a reorganization of excitatory networks following sensory perturbation. Converging evidence indicates that it is deprivation, and not an imbalance between open- and closed-eye inputs, that triggers rapid plasticity in PV neurons. However, this has not been directly tested in vivo. Using two-photon guided cell-attached recording, we examined the impact of closing both eyes for 24 h on PV neuron response properties in mouse primary visual cortex. We found that binocular deprivation induces a 30% reduction in stimulus-evoked mean firing rate and that this reduction is specific to critical period-aged mice. The number of PV neurons showing detectable tuning to orientation increased after 24 h of deprivation, and this effect was also specific to critical period-aged mice. In contrast to evoked mean firing rate and orientation tuning, measurements of trial-to-trial variability revealed that stimulus-driven decreases in variability are significantly dampened by deprivation during both the critical period and the postcritical period. These data establish that open-eye inputs are not required to drive deprivation-induced weakening of PV neuron evoked activity and that other aspects of in vivo PV neuron activity are malleable throughout life.

R01 EY-024678
critical period, vision, inhibition

Modulation of sensory ion channels by fatty acids

Valeria Vasquez [1]
(1) University of Tennessee Health Science Center, Physiology

Mechanosensitive ion channels rely on membrane composition to transduce physical stimuli into electrical signals. The Piezo1 channels mediates mechanoelectrical transduction and regulates crucial physiological processes, including vascular architecture and remodeling, cell migration, and erythrocyte volume. Whereas, Piezo2 is essential for touch discrimination, vibration, and proprioception. The identity of the membrane components that modulate Piezo channels function remain largely unknown. Using lipid profiling analyses, we here identify dietary fatty acids that tune Piezo channels mechanical response. We found that margaric acid, a saturated fatty acid present in dairy products and fish, inhibits Piezo1 and Piezo2 activation and polyunsaturated fatty acids (PUFAs), present in fish oils, modulate Piezo1 inactivation. Using atomic force microscopy, we revealed that margaric acid increases membrane bending stiffness, whereas PUFAs decrease it. We use PUFA supplementation to abrogate the phenotype of gain-of-function Piezo1 mutations (causing hemolytic anemia), and margaric acid to counteract PIEZO2 sensitization by the proalgesic agent bradykinin. Beyond Piezo channels, our findings demonstrate that cell-intrinsic lipid profile and changes in the fatty acid metabolism can dictate the cell's response to mechanical cues.

National Institute of Health, University of Tennessee Health Science Center. Piezo channels, fatty acids, Mechanosensation

Olfactory dysfunction in a prodromal Parkinson's disease model: making every sniff count

Gabriela Mercado[1], Michaela Johnson[1], Liza Bergkvist[1], Lucas Stetzik[1], Daniel Wesson[2], Patrik Brundin[1]
(1) Van Andel Research Institute, Center for Neurodegenerative Sciences, 333 Bostwick Avenue, NE, Grand Rapids, USA
(2) University of Florida, Center for Smell and Taste, 1200 Newell Dr, Gainesvill, USA

Olfactory dysfunction is a common prodromal symptom in Parkinson's disease (PD) that can develop years before the classical motor symptoms of this disease. PD pathology is characterized by the presence of intracellular aggregates that contain misfolded and post-translational modified alpha-synuclein. These alpha-synuclein pathology can be transfer from cell-to-cell and is believed that in patients can start in the olfactory bulb and from there spread across the brain leading to neuronal dysfunction and the progressive manifestation of symptoms. To study the cellular mechanism involved in this proses we develop a mouse model of prodromal PD characterized by olfactory dysfunction and alpha-synuclein pathology spreading. Using this PD model, we develop a non-invasive behavior paradigm to test olfactory dysfunction over time. And correlate this impairment with changes in neuronal survival, load of alpha-synuclein pathology and neuroimmune response. Whit this fundamental information we expect to facilitate the future development of early disease modifying intervention for PD.

NIH 5R01DC016519-04
Parkinson's disease, alpha-synuclein, olfaction.

Sensory neurons regulate C. elegans locomotion quiescence through GRK-2 signaling

Irini Topalidou[1], Michael Ailion[1]
(1) University of Washington, Biochemistry, 1705 NE Pacific street HSB #J337, Seattle, United States

G protein-coupled receptors (GPCRs) regulate diverse behaviors, including locomotion. G protein-coupled receptor kinases (GRKs) are important regulators of G protein signaling by phosphorylating activated GPCRs to terminate signaling. To further elucidate the role of GRKs in regulating GPCR-mediated locomotion, we utilized the genetic model system Caenorhabditis elegans. C. elegans has two locomotor gaits: swimming and crawling. Here we find that mutants in the C. elegans GPCR kinase GRK-2 have slow locomotion and fail to sustain body bends when swimming, suggesting that GRK-2 is a positive modulator of locomotion. We also show that GRK-2 acts on the D2-like dopamine receptor DOP-3 to inhibit Go signaling and positively modulate locomotion. Expression of GRK-2 and DOP-3 specifically in premotor interneurons mediates their effect in locomotion. Moreover, we find that mutants in GRK-2 show enhanced locomotion quiescence in a manner independent of the dopaminergic system. Using neuron-specific rescuing experiments we show that GRK-2 acts in sensory neurons to mediate this behavior. Further analysis using mutants with defects in sensory neurons indicates that sensory neurons regulate locomotion quiescence and the alert state of the animals through GRK-2 signaling. We conclude that GRK-2 modulates swimming and locomotion quiescence by acting in distinct sets of neurons.

GPCR-kinase, Sensory neurons, Dopamine signaling

SYMPOSIUM 3

Neuroscience networking and multicentric approaches to dementia research in Latin America.

Moderator: Agustin Ibañez

The Latin American Research consortium on the GEnetics of Parkinson's Disease (LARGE-PD)

Ignacio Fernandez Mata[1,2]
(1) Cleveland Clinic, Genomic Medicine Institute, Lerner Research Institute (LRI) R4-006, Cleveland, United States
(2) Case Western Reserve University, Molecular Medicine

Identification of genes that cause or increase the risk for Parkinson's Disease (PD) has enabled better prediction of at-risk individuals and has pinpointed novel targets for precision treatments. However, because the majority of studies have been conducted in European or Asian populations, little is known about the genetics of PD in Latino populations, which means millions of individuals may never benefit from advancements in personalized medicine. The Latin American Research Consortium on the Genetics of PD (LARGE-PD) encompass researchers in 35 institutions from 12 different countries, making it the world's largest PD case-control cohort of Latinos. So far our collaborators haven recruited 3,857 participants (~ 2,000 with PD), with a target to include at least 8,000 individuals by 2021 thus serving as a unique resource for genetic analysis in Latinos. Preliminary results in a small subset of LARGE-PD participants (N=1,500) already identified several novel candidate loci for PD. As LARGE-PD has progressed, several multiplex PD families (with three or more affected individuals) have been identified and enrolled, and a preliminary study has shown that about 75% of them do not carry a mutation in a known gene.We believe that including these representative populations will substantially increase the likelihood of discovering new susceptibility genes for PD. Additional benefits from this approach include: (1) providing a more rational basis for the selection of mutations for clinical genetic testing within specific geographic regions, and (2) identifying subgroups of individuals at high-risk for PD who would be good candidates for future trials.

Parkinson's Foundation, American Parkinson's Disease Association, Michael J Fox Foundation, NIH
parkinson's disease, Latin America, genetics

Naturalistic discourse as a window into neurodegeneration | Symposium: Neuroscience networking and multicentric approaches to dementia research in Latin America

Adolfo García[1,2,3]
(1) Universidad de San Andrés, Cognitive Neuroscience Center, Buenos Aires, Argentina
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Neurodegenerative diseases are growing disproportionately in Latin America, calling for innovative approaches for patient identification and severity estimations. Mainstream diagnostic, prognostic, and monitoring procedures rely on standardized clinical/cognitive tests and neuroimaging. Though irreplaceable, these approaches prove stressful, fatiguing, bound to clinician bias, and unrepresentative of everyday behavior. Also, they are often unaffordable, unfeasible, and non-viable for remote application. Aiming to circumvent these limitations, I will introduce a novel framework rooted in ecological language tasks. First, I will present studies based on automated speech assessments, showing that brief spontaneous monologues offer rich information to identify patients and predict symptom severity. Second, I will describe findings from a naturalistic text paradigm capturing disease-specific comprehension deficits and underlying neurocognitive abnormalities. The evidence obtained so far spans diverse neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, frontotemporal dementia), data collection methods (automated acoustic and textual analyses, behavioral measures, structural and functional neuroimaging, high-density electroencephalography), and statistical approaches (inferential statistics, machine learning pipelines). Overall, this approach is typified by minimal stress and fatigue, objective and consistent outcomes, high ecological validity, negligible costs, massive scalability, and direct adaptability for remote implementation. Existing findings and ongoing extensions of the framework represent a promising complement for standard approaches in clinical settings.

Global Brain Health Institute and CONICET

Neurodegenerative diseases, Cognitive markers, Languag. A Neurodegenerative Disease Landscape of Rare Mutations in Colombia Due to Founder Effects

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The contribution of genetic drift to shaping the Colombian population offers an incisive discovery platform for genotype-phenotype associations, particularly rare founder variants present today in large families. In this setting of multiple founder effects, genetic drift has enhanced deleterious variation. Nearly 1000 Colombian genomes were sequenced from individuals with early onset dementia and their relatives. Twelve pathogenic mutations causing early onset Alzheimer's from different founders were identified in PSEN1. A set of variants that underlie the clinical syndromes associated with frontotemporal dementia and amyotrophic lateral sclerosis included chromosome 9 open reading frame 72 (C9orf72), progranulin (GRN), microtubule associated protein tau (MAPT), TARDBP, FUS, VCP, FUS, CHMP2B, and TBK1. Rare variants in these genes offer novel perspectives. In addition, rare and common variants can have a small effect size for Alzheimer's disease risk and age at onset. We captured a genetic portrait of these modifier genes in the context of a powerful causative mutation—PSEN1 E280A. In this GWAS analysis, new risk factor loci were identified that explained a large proportion of the variability in age at onset. The unique demography of this population as a tri-continental admixture that passed through a severe bottleneck about 500 years ago might predict that drift would uncover rare variants with a large effect size on age at onset. Common variation was also associated with age at onset. The detection of these effects in the presence of a strong mutation for highly penetrant autosomal dominant AD reinforce the potentially impactful role of the identified variants.

dementia, genetics, Colombian population

Genetics of Alzheimer's Disease in Latin America. Recent Advances and Future studies.

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Background: A growing number of Dominantly Inherited Alzheimer Disease (DIAD) cases have become known in Latin American (LatAm) in recent years. However, questions regarding mutation distribution and frequency by country remain open.Method: A literature review was completed aimed to provide estimates for DIAD pathogenic variants in LatAm population. The search strategies were established using a combination of standardized terms for DIAD and LatAm.Result: Twenty-four DIAD pathogenic variants have been reported in LatAm countries, including 21 PSEN1, two PSEN2, and one APP variant. Our combined dataset included 3583 individuals at risk; countries with the highest DIAD frequencies were Colombia (n=1905), Puerto Rico (n=672), and Mexico (n=463), usually attributable to founder effects. AAO differed by causing gene, with a younger age at onset for individuals harboring PSEN1 variants, followed by APP and PSEN2 carriers (43.8 ±8.9 years vs 48.6 ±1.6 years vs 52.2 ±2.1 years respectively, $p<0.001$). The most common clinical presentation was amnestic. Atypical features were described with M146V-PSEN1(Argentina) and A431E- PSEN1 (Mexico) presenting with FTD-like syndrome and spastic paraparesis respectively. We found that affected individuals carrying PSEN1 mutations also experience myoclonus, pyramidal, and cerebellar signs ($p < 0.001$, $p =0.002$, and $p=0.003$, respectively).Conclusion: Future DIAD studies will be required in LatAm, albeit with a more systematic approach to include fluid biomarkers and imaging studies. Regional efforts are underway to extend the DIAD observational studies and clinical trials to Latin America.

Dominantly Inherited Alzheimer Network (DIAN, U19AG032438) funded by the National Institute on Aging (NIA) and Alzheimer's Association (SG-20-690363)

Neuroscience networking and multicentric approaches to dementia research in Latin AmericaNfl and pTau2017: Two peripheral biomarkers of Alzheimer's disease

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One of the dreams of Alzheimer's disease researchers is to find peripheral biomarkers that are useful in the preclinical diagnosis of the disease and that can be used to evaluate the effectiveness of preventive drugs and to monitor the evolution of the disease in its different states. Peripheral biomarkers have the advantage of being able to be used in most clinical settings and are less expensive than imaging biomarkers such as MRI, Amyloid-PET and Tau-PET and less invasive than cerebrospinal fluid biomarkers. In this presentation I will talk about two peripheral biomarkers in plasma: pTau217 and Neurofilaments (Nfl). Levels of pTau217 are elevated in plasma specifically in patients with mild cognitive impairment and dementia due to Alzheimer's disease, but they are also elevated in asymptomatic individuals carrying mutations in causal genes from very early stages of the preclinical phase. It is a doubly useful biomarker because it is a specific biomarker for amyloid-mediated taupathy. The biomarker is absent in plasma in people with neurodegenerative diseases other than Alzheimer's disease. The other peripheral biomarker is Neurofilments. NFL plasma levels are elevated in mild cognitive impairment and Alzheimer's disease dementia but can also discriminate between carriers and non-carriers of an Alzheimer's disease causal mutation from very early stages of the preclinical phase. Both biomarkers could become the best tool for the preclinical diagnosis and clinical follow-up of Alzheimer's disease in the coming years.

dementia, biomarkers, pTau217

SYMPOSIUM 4

Exploring key molecular determinants in pain neurophysiology.

Moderator: Rodolfo Madrid-Elias Utreras

Role of Kv1.6 in blocking hyper excitability after nerve injury (Rol de los Kv1.6 en la hiperexcitabilidad de neurona sensorial luego de daño axonal)

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Neuropathic pain following nerve injury is associated with hyperexcitability in damaged myelinated sensory axons, which normalises over time. We previously showed in rats that after nerve injury Kv1 channel expression at the juxtaparanode decreases acutely, but when hypersensitivity wanes and pain decreases, the Kv1.6 channels is expressed de novo.We now examined the functional effect of altered Kv1 subunit composition on axonal excitability and neuropathic pain.For this, we set up rat sensory neurons cultures and performed an axotomy once the axons have myelinated. After axotomy Kv1.2 expression was decreased while Kv1.6 was increased. Calcium imaging showed an increased basal level acutely after axotomy that returned to normal after a fortnight. We registered actions currents in these axons using cell-attached voltage-clamp and observed an increased rate of spontaneous firing in acute axotomy that reversed with time. We are working on blocking and overexpressing Kv1.6 to investigate changes in spontaneous activity. In the same line, we used a neuroma model of neuropathic pain in rats, in which hypersensitivity develops after nerve damage and reverses in 3 weeks. At this time, we injected the Kv1.6 blocker CPY-Fe1 and observed a similar reduction of mechanical thresholds as seen after axotomy. These results indicate that Kv1.6 which is expressed in late but not acute axotomy, plays a role in regulating axonal excitability after damage.In conclusion, changes in the molecular composition and distribution of axonal Kv1 channels, represents a protective mechanism to suppress the hyperexcitability of myelinated sensory axons that follows nerve injury.

Fondecyt 1161019
neuropathic pain, kv1.6, sensory neuron excitability

Regulation of the P2X2 receptor channel by calcium and phosphorylation by Cdk5 and its potential role on pain signaling (Regulación del receptor P2X2 por calcio y fosforilación por Cdk5 y su potencial rol en la señalización del dolor)

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The purinergic P2X2 receptor (P2X2R) is an ATP–gated ion channel widely expressed in the nervous system. In this talk, I will briefly describe the use-dependent desensitization (UDD), that consists in a progressive increase in receptor desensitization during repetitive agonist application. This phenomenon is calcium-dependent and also depends on intracellular ATP, a mechanism that involves phosphorylation of intracellular P2X2R residues. Next, I will focus on the regulation of P2X2aR by cyclin-dependent kinase 5 (Cdk5) phosphorylation. We identified a putative site in the full-size variant P2X2aR (372TPKH375), which is absent in the splice variant P2X2bR. An interaction between P2X2aR and Cdk5/p35 was observed by co-immunofluorescence and co-immunoprecipitation. Moreover, threonine phosphorylation was significantly increased in HEK293 cells co-expressing P2X2aR and p35. P2X2aR-derived peptides containing the Cdk5 consensus motif were phosphorylated by Cdk5/p35. Electrophysiological recordings indicated a delay in development of UDD of P2X2aR/Cdk5 but not of P2X2bR/Cdk5 in HEK293 or Xenopus oocytes. A similar effect was found in P2X2a/3R heteromeric currents. The P2X2aR-T372A mutant was resistant to UDD. In endogenous cells, we observed P2X2R/Cdk5/p35 interactions by co-localization using immunofluorescence in primary culture of nociceptive neurons, and by co-immunoprecipitation in mouse trigeminal ganglia. Finally, endogenous P2X2aR-mediated currents in PC12 cells and P2X2/3R mediated increases of [Ca2+]i in trigeminal neurons were Cdk5-dependent, since inhibition with roscovitine accelerated the desensitization kinetics of these responses. These results indicate that the P2X2aR is a novel target for Cdk5-mediated phosphorylation, which might play important roles including in pain signaling.

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P2X2, Cdk5, Pain

Regulation of TRPM8 channels by phosphorylation (Regulación del canal TRPM8 por fosforilación)

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TRPM8 is the main molecular entity responsible for detection of cold temperatures in the somatosensory system. This calcium-permeable cation channel is activated by cold, cooling compounds such as menthol, voltage and osmolality rises. It has been suggested that TRPM8 function could be regulated by phosphorylation. To explore the mechanism underlying this regulation, we evaluated the contribution of this posttranslational modification (PTM) in TRPM8 function in both recombinant systems and cold thermoreceptor neurons. By mass spectrometry, we identified 4 serine residues within the N-terminus constitutively phosphorylated. TRPM8 function examined by Ca2+-imaging and patch-clamp analysis, revealed that pharmacological pan-inhibition of kinases causes an important increase in cold- and menthol-evoked responses of TRPM8, suggesting that a constitutive phosphorylation acts as a negative modulator of the channel. We also found that the activation of protein kinase C (PKC) allows the recruitment of new phosphorylation sites, and reduces the maximal response of TRPM8 to cold and menthol, causing a shift in the temperature threshold of cells expressing TRPM8 channels to lower temperatures. Both basal kinase and PKC activity also downregulate TRPM8 function in CTNs, suggesting that cold sensing could be fine-tuned by controlling its phosphorylation state, an observation also accounted for by mathematical modeling. Our results shed light on the molecular bases of TRPM8 regulation by this dynamic and reversible PTM, suggesting that alterations of TRPM8 phosphorylation status could be playing a role in painful pathologies states such as cold hypersensitivity and dry eye disease.

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Cold transduction, primary sensory neurons, dry eye

Glycine receptor modulation in chronic pain (Modulación de receptores de glicina en dolor crónico)

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Diminished inhibitory glycinergic neurotransmission on the spinal dorsal horn contributes to the development and maintenance of chronic pain. A PGE2-mediated PKA-dependent phosphorylation of glycine receptors containing the alpha3 subunit (α3GlyRs) is particularly relevant for the development of pain hypersensitivity. Restoring the activity of α3GlyRs through positive allosteric modulators (PAMs) may constitute a rational approach against chronic pain. In addition, modulators that increase the activity of α3GlyRs in the phosphorylated state may specifically reverse the loss of neuronal inhibition. However, our current understanding of the molecular events involved in the malfunction of α3GlyRs in the phosphorylated state and of the actions of PAMs in these altered GlyRs is very limited. We have explored several aspects of these issues by using electrophysiological recordings in combination with behavioral studies and novel PAMs. Using site-directed mutagenesis, optical tools, and single-channel recordings, we demonstrate that the PKA-mediated phosphorylation of α3GlyRs diminished the channel ion conductance. We found in addition that the modulation of α3GlyRs by PAMs is influenced by the phosphorylation state. Interestingly, we found that a particular PAM (i.e. 2,6-DTBP) normalized the impaired conductance of phospho-mimetic α3GlyRs. In other set of studies, we found that 2,6-DTBP enhanced dorsal horn α3GlyRs in the phosphorylated state and showed anti-hyperalgesic effects in behavioral pain models. Collectively, our findings propose a molecular framework for a pain sensitization mechanism and suggest that the positive allosteric modulation of α3GlyRs alleviates chronic pain, at least in part, through the restoration of chloride conductance of phosphorylated GlyRs.

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chronic pain, glycine receptor, phosphorylation.

SYMPOSIUM 5

Young Neuroscientist

Moderator: Patricio Orio

Palmitic Acid Inhibits Autophagic Flux and Ciliogenesis Impairing Insulin Signaling in Hypothalamic Neurons

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Palmitic acid (PA) is accumulated in the hypothalamus of mice after the consumption of a high-fat diet. Autophagy is required for the formation of the primary cilium (PC) or ciliogenesis. Inhibition of autophagy, as well as PC depletion in hypothalamic neurons, triggers obesity and insulin resistance in mice. Our aim was to evaluate whether the PA dependent inhibition of autophagic flux inhibits ciliogenesis and decreases insulin sensitivity. Methods: primary cultures of hypothalamic neurons and N43/5 cells were treated with PA or vehicle (BSA) in the absence or presence of Bafilomycin A1 to evaluate autophagic flux by Western blot (WB) and Immunofluorescence (IF). The percentage of ciliated cells and PC length were determined by IF. Insulin-induced Akt phosphorylation was evaluated by WB. We demonstrated exposure of hypothalamic neurons to PA inhibits the autophagic flux and reduces both the percentage of ciliated cells and PC length. Pharmacological or genetic inhibition of autophagy decreases PC expression and, conversely, depletion of PC modulates autophagy. The insulin signaling following PA treatment, autophagy inhibition, or PC depletion was reduced suggesting PA impairs ciliogenesis through the inhibition of autophagic flux thereby reducing insulin sensitivity in hypothalamic neurons. This work demonstrates crosstalk between autophagy and PC in hypothalamic neurons.

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Primary cilium, Autophagy, Saturated Fatty Acids

Nicotinic receptor triggered exocytosis in chromaffin cells requires activation of P2X7 receptors by an autocrine ATP mediated mechanism

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Chromaffin vesicles, apart from releasing the stress hormones adrenaline and nor-adrenaline, contain diverse molecules that are co-secreted and regulate exocytosis in an auto-paracrine manner (Herrero et al., 2002; Ennion et al., 2004). Among these is ATP, which is stored at high concentrations in secretory vesicles (~150 mM, Winkler and Westhead, 1980). Interestingly, recent studies have shown that co-released ATP is able to generate P2X4-dependent currents in adjacent patched sniffer cells (Xiong et al 2018; Zhang et al 2019). Here, we sought to determine by amperometry whether ATP co-released during Ca2+ dependent exocytosis affects, in an autocrine manner, secretion in chromaffin cells. Our results indicated that in the presence of the ATP degrading enzyme apyrase, exocytosis was almost abolished and the exocytosis kinetics was altered delaying the expansion and decreasing the permeability of the nascent fusion pore. We hypothesized that a receptor activated by high ATP concentrations could be involved. Thus, by pharmacological inhibition, we found that the P2X7 receptor seems to be activated to potentiate nAChR-induced secretion and regulate fusion pore dynamics. This finding was corroborated using P2X7 KO mice, wherein genetic deficiency of the channel negatively altered nAChR-elicited exocytosis. Finally, experiments in Fura-2-loaded cells suggest that P2X7 controls vesicle fusion through a mechanism that is not dependent upon cytosolic Ca2+ signals. Our results points to the P2X7r as a novel participant in exocytosis, and as such its study would prove relevant to understand diverse physiological process wherein neuro-secretion is altered.

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Exocytosis, P2X7, Nicotinic receptor

Mab21l2 links morphogenesis and differentiation in developing zebrafish eyes (Mab21l2 conecta morfogenesis y diferenciacion durante el desarrollo de los ojos en pez cebra)

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Shaping the vertebrate eye requires evagination of the optic vesicles. These vesicles subsequently fold into optic cups prior to undergoing neurogenesis and allocating late progenitors at the margin of the eye, in the ciliary marginal zone (CMZ). mab21l2 encodes a protein of unknown biological function expressed in the developing visual system, and loss of mab21l2 function results in malformed eyes. The bases of these defects are, however, poorly understood. To study mab21l2 we used CRISPR/Cas9 to generate a new zebrafish mutant allele (mab21l2u517). We characterized eye morphogenesis and neurogenesis upon loss-of-mab21l2 function using tissue/cell-type-specific transgenes and immunostaining, in situ hybridization and bromodeoxyuridine incorporation. mab21l2u517 eyes fail to grow properly and display an excess of progenitors in the CMZ. The expression of a transgene reporter for the vsx2 gene –a conserved marker for retinal progenitors– was delayed in mutant eyes and accompanied by disruptions in the epithelial folding that fuels optic cup morphogenesis. Mutants also displayed nasal-temporal malformations suggesting asynchronous development along that axis. Consistently, nasal retinal neurogenesis initiated but did not propagate in a timely fashion to the temporal retina. Later in development, mutant retinas did laminate and differentiate. Thus, mab21l2u517 mutants present a complex eye morphogenesis phenotype characterized by an organ-specific developmental delay. We propose that mab21l2 facilitates optic cup development with consequences both for timely neurogenesis and allocation of progenitors to the zebrafish CMZ. These results support a role of mab21l2 in coordinating morphogenesis and differentiation in developing eyes.

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morphogenesis, differentiation, eye.

Breaking models: Optogenetic activation of the inhibitory nigro-collicular pathway evokes paradoxical contralateral orienting movement in mice (Rompiendo modelos: Activacion por optogenetica de la via inhibitoria nigro-collicular produce un movimiento contralateral paradojico en ratones.)

Claudio Villalobos Dintrans[1], Michele Basso[1]
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The current model for controlling movement initiation proposes that the basal ganglia (BG) plays a permissive role in the generation of movements through the modulation of the amount of inhibition on BG target structures such as the superior colliculus (SC), a key structure involved in orienting control. One of the outputs of the BG, the substantia nigra pars reticulata (SNr), contains GABAergic neurons that project to the ipsilateral SC. The current model suggests that removal of SNr inhibition, combined with cortical excitatory drive into the SC, produces contralateral orienting movements. This model of action is referred to as the rate model, where the rate of inhibitory spiking onto target structures is what determines the initiation of movement; high rates and inhibition prevent movement, while low rates and less inhibition produces movement. We tested this hypothesis by optogenetically controlling the rate of SNr activity into the SC. Contrary to the model predictions, optogenetic activation of the SNr terminals into the SC of mice evoked, rather than prevented, contralateral movement. To determine how orienting movements may result from the activation of inhibitory terminals, we performed a series of slice experiments and found that the same optogenetic stimulation evoking contralateral movements in vivo evoked post-inhibitory rebound depolarization and spiking in the SC output neurons. These results challenge the current view regarding the role of the nigro-collicular pathway in the initiation of orienting movements and may provide new understanding on the progression and pathophysiology of movement disorders associated with the function of the BG.

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Motor control, superior colliculus, basal ganglia

SYMPOSIUM 6

Current Topics on Language Neural Processing.

Moderator: Rocio Loyola-Navarro and Ana Campos Espinoza.

Word learning in two languages: Neural overlap and representational differences

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We investigated the neural basis of newly learned concepts and words in Spanish as a mother tongue (L1) and English as a second language (L2). Participants acquired new names for real but unfamiliar concepts in both languages over the course of two days. On day 3, they completed a semantic categorization task during fMRI scanning. The results revealed largely overlapping brain regions for newly learned words in Spanish and English. However, Spanish showed a heightened BOLD response within prefrontal cortex (PFC), due to increased competition of existing lexical representations. In contrast, English displayed higher activity than Spanish within primary auditory cortex, which suggests increased phonological processing due to more irregular phonological-orthographic mappings. Overall, these results suggest that novel words are learned similarly in Spanish L1 and English L2, and that they are represented in largely overlapping brain regions. However, they differ in terms of cognitive control and phonological processes.
This work was supported by Agencia Nacional de Investigación y Desarrollo (ANID), Chile [Fondecyt grants 11130678 and 1200268] to Roberto Ferreira. Gabriella Vigliocco was supported by a Royal Society Wolfson Research Merit Award.

Word learning, bilingualism, fMRI

Natural language syntax, active inference and the hidden states of the world

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I will outline the current state-of-the-art knowledge of the electrophysiological basis of natural language syntax. Broadly, this involves a range of low frequency components modulating fast broadband gamma cross-cortical activity, indicating local representational processing. I will relate these models of syntax to the concepts of active inference and free energy. I will suggest that the existence of syntactic structures in natural language constitutes a unique form of epistemic foraging, minimizing surprise and variational free energy. Epistemic foraging aims to reduce uncertainty about the environment, a role fulfilled by lexical categories and syntactic composition.
syntax, free energy, oscillations

The linguistic infant brain .Current topic on neural language processing

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Humans learn their native language in an apparently effortless way. Such learning starts at the womb. During the first year the infants learn about the sounds of their native language, by their first birthday they comprehend ~100 familiar words and have a rudimentary notion of the typical shape of native words and grammar, and by the 2nd year toddlers start to speak making complex sentences that they have never heard. Such rapid learning would emerge from prior knowledge and experience, which the infant brain reflect by structural and functional reorganization. This presentation will update some points about this brain reorganization during early infancy.

Project # ID16I20210
language acquisition, brain

Language Lateralization during language recovery post stroke and due to a brain tumor

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In the presence of a brain tumor, the hemispheric dominance needs to be established as accurately as possible to reduce the risk of postoperative language deficits. Language localization in the brain varies among individuals and specifically varies with handedness. With specific language tasks, language activation can be explored not only in classical language areas localized in supratentorial regions of the brain but also in the cerebellum. The cerebellar language activation is generally undisturbed by the tumor localized in or near the presumed classical language areas; thus, it may be of interest as an additional diagnostic feature to determine language dominance in brain tumor patients. Behavioral studies have widely assessed language disturbances in stroke patients with aphasia, characterizing their initial language profile and recovery process. Functional MRI offers a unique possibility to study the process of recovery on a neurophysiological level by assessing the plasticity of the nervous system during the recovery process. Functional MRI studies of language recovery in aphasic patients can provide further insights into how language activation changes during spontaneous recovery or in response to specific language therapy. Keywords (1) Aphasia, (2) fMRI, (3) plasticity.

SYMPOSIUM 7

Recent experimental designs to discover effective therapies to treat epilepsy.

Moderator: Juan Carlos Saéz

c-Abl signaling inhibition prevents neurons damage and seizures induction in temporal lobe epilepsy (La inhibición de la señalización de c-Abl previene el daño neuronal y la inducción de convulsiones en la epilepsia del lóbulo temporal)

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Temporal lobe epilepsy (TLE) is characterized by spontaneous seizures caused by neuronal circuits hyperexcitability that stimulate excessive release of glutamate, inducing excitotoxic damage of neurons in the hippocampus. However, the molecular mechanisms that drive the development of TLE remain elusive. Previously we reported that cAbl kinase activation modulates apoptosis and synaptotoxicity in neurodegenerative diseases. Here, we show that cAbl inhibition prevented apoptosis, reduced dendritic spine loss, and maintained phosphorylation of NMDA receptor subunit 2B (NR2B) in in vitromodels of excitotoxicity. Furthermore we found that the tyrosine kinase cAbl plays a key role in seizures induction in TLE. Using a pilocarpine-induced mouse model of TLE, we observed that disrupting cAbl activity using small molecule inhibitors or a genetic knockout led to fewer seizures, increased latency towards the status epilepticus and improved animal survival. Because cAbl inhibitors currently in clinical use are non-selective and have poor brain penetration, we developed a new allosteric cAbl inhibitor, with favorable potency, selectivity, pharmacokinetics, and vastly improved central nervous system permeability. Neurons treated with the new c-Abl inhibitor exhibited less cell death upon direct NMDA exposure, and mice fed a diet containing c-Abl inhibitor had fewer seizures and improved survival following TLE induction with pilocarpine. Overall, we reveal that cAbl kinase regulates NR2B-NMDAR to mediate response to excitotoxicity and TLE, and introduce a new selective, brain-penetrant, allosteric inhibitor of cAbl for the potential treatment of epilepsy.

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c-Abl, Epilepsy, pilocarpine

Pentylenetetrazol elevates the membrane permeability of hippocampal glia and neurons and their blockade prevent seizures (El pentilenetetrazol eleva la permeabilidad de la membrana de las glías y neuronas del hipocampo y su bloqueo previene las convulsiones)

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Epilepsy treatments target specific neurons and are only symptomatic. A few recent studies have proposed glial cells as molecular targets. Here, we show that increased neuronal activity promotes activation of glial connexin hemichannels (Cx HCs), which plays a critical role in neuronal hyperactivity. Adult C57BL/6 male mice were treated with pentylenetetrazol (PTZ), an epileptogenic compound that blocks GABAA receptors. The hemichannel activity was evaluated using the ethidium uptake assay (Etd+, "snapshot") in hippocampal neurons and glial cells identified by their content of molecular markers (confocal immunofluorescence). Cx HCs were blocked with a small organic molecule called D4. The electrical activity hippocampal neuron population in hippocampal slices was evaluated using a multi (252) electrodes array (MEA) set up. Behavioral observation shows mice with evident seizures at ~6 min post PTZ administration, followed by several hours, in which they showed very low motor activity, sporadic convulsions, and only ~69% of them survived. Within 30 min post-PTZ administration, the Etd+ uptake increased in a time- and cell type-dependent manner. However, mice pretreated with D4 showed only the initial convolutions at ~6 min post-PTZ administration and the Etd+ uptake of all cells remained as in control mice. During the following hours, PTZ-treated mice behaved as control mice and evolved with 100% survival. D4 also prevented the PTZ-induced electrical activity and dye uptake in cells of ex-vivo hippocampal slices treated with PTZ. Consequently, blockade of Cx HCs with small organic molecules could be an alternative and/or a complementary way to improve current treatment of epilepsy.

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connexons, microglia, astrocytes

Distinct contributions of neuronal and astrocyte pannexin1 to seizures.

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Studies from our group and others provided strong evidence supporting a role for purinergic-mediated signaling via Panx1 channels in seizures. In the kainic acid (KA) model of seizures, global deletion or blockade of Panx1 channels reduces the duration of status epilepticus (SE) and the frequency of spontaneous seizures, which are paralleled by decreased levels of extracellular ATP. To gain insights into the relative contribution of astrocyte vs neuronal Panx1 to seizures, transgenic mice with astrocyte (GFAP-Cre) and neuronal (NFH-Cre) targeted deletion of Panx1 were used to investigate the impact of these channels on KA-induced acute seizures. Clinical scoring of seizures indicated that the onset of bilateral forelimb clonus in mice lacking astrocyte Panx1 was faster while those lacking neuronal Panx1 was delayed compared to control (Panx1f/f) mice. Electroencephalographic recordings confirmed that the progression of seizures (from first spike to SE) was delayed in mice lacking neuronal Panx1 and accelerated in mice lacking astrocyte Panx1. Immunohistochemistry and western blot analyses from brains of mice after SE revealed increased expression levels of adenosine kinase (ADK), an enzyme that regulates extracellular levels of adenosine, in mice lacking astrocyte Panx1. Thus, the worsening of seizures seen in mice lacking astrocyte Panx1 is likely related to decreased adenosinergic signaling due to the increased ADK levels in astrocytes. In contrast, in mice lacking neuronal Panx1, enhanced adenosinergic signaling due to rise of extracellular adenosine levels derived from enzymatic degradation of ATP released by astrocytes and by the efflux of adenosine from astrocytes could delay SE onset.

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seizures, pannexin

Sensory neurons regulate C. elegans locomotion quiescence through GRK-2 signaling

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G protein-coupled receptors (GPCRs) regulate diverse behaviors, including locomotion. G protein-coupled receptor kinases (GRKs) are important regulators of G protein signaling by phosphorylating activated GPCRs to terminate signaling. To further elucidate the role of GRKs in regulating GPCR-mediated locomotion, we utilized the genetic model system Caenorhabditis elegans. C. elegans has two locomotor gaits: swimming and crawling. Here we find that mutants in the C. elegans GPCR kinase GRK-2 have slow locomotion and fail to sustain body bends when swimming, suggesting that GRK-2 is a positive modulator of locomotion. We also show that GRK-2 acts on the D2-like dopamine receptor DOP-3 to inhibit Go signaling and positively modulate locomotion. Expression of GRK-2 and DOP-3 specifically in premotor interneurons mediates their effect in locomotion. Moreover, we find that mutants in GRK-2 show enhanced locomotion quiescence in a manner independent of the dopaminergic system. Using neuron-specific rescuing experiments we show that GRK-2 acts in sensory neurons to mediate this behavior. Further analysis using mutants with defects in sensory neurons indicates that sensory neurons regulate locomotion quiescence and the alert state of the animals through GRK-2 signaling. We conclude that GRK-2 modulates swimming and locomotion quiescence by acting in distinct sets of neurons.

GPCR-kinase, Sensory neurons, Dopamine signaling

SYMPOSIUM 8

A Round Trip to Metabolism and Cognition

Moderator: Jimena Sierralta

Perfect homeostasis: on the verge of death 4 times per second, for 100 years (Homeostasis perfecta: al borde del colapso metabólico cada 4 segundos, por 100 años.)

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Neurons are subject to sudden functional demands that push their consumption of energy by large factors. Neurons do not have energy stores and lie deep in the parenchyma, isolated from blood-borne fuel (glucose) by two cell layers. When energy production falls behind consumption, neurons undergo metabolic stress, which leads to cumulative oxidative damage, degeneration and death. Still, most neurons stay healthy till old age. How is survival accomplished in the face of such unpredictable environment?Experiments in our group show that neurons possess an intrinsic machinery that couples ATP consumption and production (Baeza-Lehnert et al., Cell Metabolism 2019). This mechanism has a limited dynamic range, over which there is Ca2+, Na+, and H+ deregulation, mitochondrial stress and ATP depletion. Sitting in a higher echelon are glial cells like astrocytes and oligodendrocytes, which deliver glucose, lactate and oxygen on demand and modulate neuronal activity, possibly explaining the observed trade-off between neighboring circuits.Regardless of intrinsic and glial protection, if neurons are stimulated beyond their metabolic capability, they will suffer. So how is this all-important homeostatic range defined? Is it written in the genes or are neurons metabolically trained during development, or perhaps also after development? Do neurons control their own metabolic fate by feeding back on their upstream network? and, could it be that the output and design of the neuronal network is shaped by energy constraints? After all, our oversized primate brain evolved in a context of chronic food shortage, witness the positive selection of thrifty genes.

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Brain energy, neuron, lactate

Is behavior a consequence of the energetic homeostasis of neural circuits?

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A major goal of neuroscience is understanding how neurons arrange themselves into neural networks that result in behavior. Most theoretical and experimental efforts have focused on a top-down approach which seeks to identify neuronal correlates of behaviors. Nonetheless, these approaches have only implicitly considered the fact that neural tissue, like any other physical system, is subjected to several restrictions and boundaries of operations.We recently proposed the Energy Homeostasis Principle (Vergara et al; 2019), where the balance between energy income, expenditure, and availability are the key parameters in determining the dynamics of the found neuronal phenomena from molecular to behavioral levels. Neurons display high energy consumption relative to other cells. The largest energy, by far, is expended by action potentials and post-synaptic potentials; therefore, plasticity can be reinterpreted in terms of their energy context. Consequently, neurons, through their synapses, impose energy demands over post-synaptic neurons in a close loop-manner, modulating the dynamics of local circuits. Subsequently, the energy dynamics end up impacting the homeostatic mechanisms of neuronal networks. Furthermore, local energy management also emerges as a neural population property, where most of the energy expenses are triggered by sensory or other modulatory inputs. Local energy management in neurons may be sufficient to explain the emergence of behavior. Vergara RC, Jaramillo-Riveri S, Luarte A, Moënne-Loccoz C, Fuentes R, Couve A, Maldonado PE. (2019) The Energy Homeostasis Principle: Neuronal Energy Regulation Drives Local Network Dynamics Generating Behavior. Front Comput Neurosci. 13:49. doi: 10.3389/fncom.2019.00049.

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Behavior, Brain-energy, Simposio

Transfer of metabolites from glia to neurons an evolutionary conserved mechanism to fuel the brain activity.

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It is known that the nervous system has a high energy cost compared to other tissues of the organism, including the heart and the somatic muscle. The knowledge of the cellular components that more importantly contribute to the energy expenditure suggest that the synapse is proportionally the most costly. If we consider that there are at least 1000 times more synapses that neurons in the central nervous system is clear that to understand the impact of the energy management, we have to focus on the synapse where the pre and postsynaptic compartments require ionic transport mechanisms that are dependent of ATP allowing the maintenance of the ionic gradients. ATP necessities are multiplied many times during neuronal activity potentially generating limitation to it, unless mechanisms such as increasing supplies of glucose and oxygen are set in place. Thus, limitations in all nervous systems include the access to the vascular system that provides these molecules as well as the barriers that they need to traverse to reach the synapse such as the astrocytes that surround the synaptic terminals. I will discuss literature as well as data from my lab* that show the importance of the glia that surrounds the synaptic terminals for the energy requirements in the synapse during high frequency activity. A comparison between vertebrate and invertebrate brains will also set the basis for discussing the limitations to the function, independent of its organization.*González-Gutierrez, A., Ibacache, A., Esparza, A, Barros, LF, Sierralta, J#. Glia 2020, DOI: 10.1002/glia.23772

Biomedical Neuroscience Institute, BNI ICN09_015
Brain-energy, Glia, Lactate

What is the behavioral-level explanatory role of neural metabolic efficiency?

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A way in which ATP availability can be connected to behavioral level explanations is through interpretative models, which explain why a system produces a phenomenon through a specific processing strategy. In these models, ATP defines a demand or design variable and the implementation of a given processing strategy can be explained in terms of its contribution to the optimization of that variable. Within this approach, any level of mechanistic organization (including behavior) could be potentially shaped by energy demands. In this vein, the Energy Homeostasis Principle posits that energy income, expenditure, and availability are the key parameters determining the dynamics of neuronal phenomena from molecular to behavioral levels. I would like to examine the behavioral level application of the principle, which relies on the 'active inference' framework. Under this view, neural feedforward signals only respond to prediction error and the minimization of this variable is the driving force of behavior. Thus, when behavior minimizes prediction error by producing expected stimuli, it reduces processing cost (therefore contributing to energy homeostasis) by decreasing the amount of action potentials generated by feedforward channels and the redundancy of sensory signals. However, it has been suggested that prediction requires to explicitly encode the statistical correlations between environmental stimuli (i.e., sensory redundancies), which results in a metabolically expensive code. If this were the case, it may not be possible to explain the fact that behavior is driven by the goal of predicting incoming stimuli in terms of its contribution to energy homeostasis.

Proyecto Fondecyt 3180468
brain-energy, active-inference, redundant neural codes

ORAL COMUNICATIONS I

Uncovering the genetic basis underlying sleep abnormalities in Parkinson's disease Uncovering the genetic basis underlying sleep abnormalities in Parkinson's disease

Uncovering the genetic basis underlying sleep abnormalities in Parkinson's disease Uncovering the genetic basis underlying sleep abnormalities in Parkinson's disease

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Disease (PD) is the second neurodegenerative disease with the highest prevalence globally, affecting 1% of the population above 60 years old. 85% of PD cases are idiopathic (iPD) and cannot be related to a mendelian inheritance pattern. PD patients present the degeneration of dopaminergic neurons at the substantia nigra leading to several motor and non-motor symptoms. Sleep disturbances, including idiopathic REM sleep behavior disorder (iRBD), precede PD's clinical onset by months or even years before any motor symptoms appear. Patients experience vocalization, jerks, and motor behaviors during REM sleep, together with sleep fragmentation and insomnia. To uncover the genetic basis of underlying sleep perturbations in iPD, we exposed Drosophila to Rotenone, a validated model of iPD neurodegeneration. We used the Drosophila Genetic Reference Panel (DGRP), a collection of 205 sequenced isogenic lines representing a natural population's genetic variation, allowing the association between genotype and sleep traits. We found that DGRP lines under Rotenone treatment show significant variation in sleep behavior. Using genome-wide association studies, we identified 345 single nucleotide polymorphisms that mapped to 233 genes potentially associated with iPD-related sleep disorders . Interestingly, human orthologs of 29 of such genes, including Glucocerebrosidase (GBA), whose mutations are the major genetic risk factor of iPD, are associated with iRBD. Our work proposes novel modifier genes of the sleep disturbances that precede the development of PD and could help to predict the outcome of the disease and the design of personalized therapies. Pew Innovation Fund #00032422; ICM P09-015F, BNI Keywords (1) Parkinson's disease, (2) sleep, (3) GWAS.

Dlg y dPMCA presináptico interactúan y regulan la liberación asincrónica y espontánea, en la unión neuromuscular de larvas de Drosophila melanogaster.

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Neurotransmitter release in the synapse occurs at electron-dense estructures called active zone. The amount and timing of the released neurotransmitters at the active zone depends in one part on the entry of Ca2+ through voltage-dependent calcium channels (VDCC), and also of Ca+2 extrusion mechanisms. In D. melanogaster, the main mechanism of bulk Ca+2 extrusion in presynaptic terminals is the plasma membrane calcium pump (dPMCA). dPMCA has a C-terminal PDZ interaction motif, which allows the interaction with PDZ containing proteins like Dlg-MAGUK scaffolds proteins. We hypothesize that Dlg control dPMCA membrane abundance and localization, impacting the calcium extrusion and the neurotransmitter release kinetics in motoneurons of D. melanogaster NMJ. Using antibodies and genetic reporters for dPMCA we observed defects in dPMCA localization in pre and postsynaptic membrane of the NMJ in dlg mutant larvae. Using STED microscopy, we were able to observe Dlg and dPMCA presynaptic distribution in clusters along presynaptic membrane and the disruption of dPMCA clustering n DlgS97 mutant animals. Upon dlg knockdown only in the presynaptic compartment, we observed that the mEPSC frequency at physiological resting conditions as well as the asynchronous release frequency after a period of high frequency stimulation (150 stimuli at 20Hz) was increased. We demostrate that Dlg and dPMCA interact between them and this interaction plays a role for the regulation of the calcium kinetics extrusion and neurotrasmitter release under resting and after synaptic activity at the Drosophila NMJ. - Beca doctorado nacional 2016-2020, > ANID - Conicyt (Ministerio de Ciencia, Tecnología e Innovación) - Biomedical Neuroscience institute (BNI) > ICN 09_015. - Fondecyt 1171800 > “Presynaptic calcium signal in glutamatergic synapses: role of scaffold proteins on its modulation” Keywords (1) Calcium extrusion, (2) Drosophila NMJ, (3) Presynaptic Dlg and dPMCA

The Neuron-Astrocyte Functional Unit During Brain Aging The Neuron-Astrocyte Functional Unit During Brain Aging

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Aging is a major risk factor for age-associated disease, like cancer and neurodegenerative disorders. While advances have been made on events after cognitive decline or disease onset, the study of mechanisms underlying normal brain aging, and how they become a risk factor for disease are not well understood. In this context, how the astrocyte-neuron interaction changes during aging has not been extensively studied, although this is key for neurotransmission. Altered intercellular communication is a hallmark of aging, and astrocytes secrete molecules required for neuronal function. We combined bioinformatics and computational modeling to identify age-associated changes in the astrocyte-neuron unit that could affect functional decline observed with aging. We analyzed transcriptomic data of mouse astrocyte and neuron aging and identified 201 putatively secreted proteins by astrocytes differentially expressed during aging. Interestingly, among them were genes involved in KEGG pathways also enriched during neuronal aging: e.g., 'Alzheimer's disease' and 'Pathways in cancer'. We next analyzed metabolic coupling of the neuron and astrocyte by developing a novel approach that combined graph theory with flux balance analysis to identify the most relevant nodes (mostly metabolic reactions), required for successful neurotransmission. Genes associated with these reactions were found differentially expressed in neurotransmission transcriptomic databases. Interestingly, we also found genes like hmgcs2 and aacs, related to ketone body synthesis, that were also found differentially expressed during astrocyte aging. We propose that using our approach, age-associated changes in the astrocyte-neuron unit, relevant for disease etiopathology can be identified and help identify novel therapeutic targets. FONDAP Geroscience Center for Brain Health and Metabolism (15150012 to CGB); FONDECYT Postdoctoral (3180180 to DLL; 3200726 to AA). Keywords (1) brain aging, (2) astrocyte aging, (3) neuronal aging.

Functional Changes on the Retinal Ganglion Cells in a Mouse Model of Alzheimer Disease Are Linked with Neurotransmitters Alterations Functional Changes on the Retinal Ganglion Cells in a Mouse Model of Alzheimer Disease Are Linked with Neurotransmitters Alterations

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Purpose: To determine whether the 5xFAD mouse, a model of Alzheimer's disease (AD), shows changes in the expression of glutamate (Glu) and gamma-aminobutyric acid (GABA) neurotransmitters and in the physiology of the retinal ganglion cells (RGCs) during the temporal course of AD. Methods: Retinas from youngs (2-3 months, n=20) and adults (6-7 months, n=20) 5xFAD and WT mice were employed. For each animal, one eye was collected and fixed for immunogold-silver staining to detect Glu and GABA in the retina, and RGCs activity was recorded using a multielectrode array under different stimulus conditions from the contralateral eye. All methods used here are in compliance with bioethical certification. Results: Glu was predominantly visualized in the RGC layer in youngs and adults 5xFAD, but not in the young or adults WT. GABA was predominantly found in the highest level in the inner retina in young and adults 5xFAD in comparison to WT. In scotopic and photopic conditions, the firing rate and burst from RGCs were higher in youngs 5xFAD compared to youngs WT while adults 5xFAD shows lower values compared to the adults WT. Conclusions: We reported changes in Glu and GABA on the retina layers for 5xFAD mice retinas and concomitant upregulation of the RGCs physiology for spontaneous scotopic and photopic activity in the youngs 5xFAD and downregulation on adults 5xFAD. Our results suggest hyperactivity from RGCs in the early stages of the disease and hypoactivity in the latest stage of the pathology and this is depending on illumination condition. Dr. Araya was supported by ANID Ph.D. scholarship # 21171156. Dr. Palacios is supported by FONDECYT-ANID #1200880, ICM-ANID #P09-022-F, CINV. Dr. Chacón is supported by FONDECYT-ANID #1181659. Dra. Durán-Aniotz is supported by Alzheimer's Association Research Grant 2018-AARG-591107. Dra. Escobar is supported by AFOSR Grant Nro. FA9550-19-1-0002. Keywords (1) Alzheimer disease, (2) retinal ganglion cells, (3) electrophysiology.

Automated detection of REM sleep motor events based on the envelope analysis of the electromyogram: a study in microdeletion 22q11.2 syndrome patients. (Detección automática de eventos motores del sueño REM basado en el análisis de la envolvente del EMG: estudio en pacientes con síndrome de microdeleción 22q11.2.)

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Introducción: La parálisis fisiológica de sueño REM impide que los sujetos "actúen el sueño". Lesiones neurodegenerativas en tronco encefálico (alfa-sinucleinopatías, como Enfermedad de Parkinson) pueden impedir la parálisis del sueño REM generando el Trastorno Conductual del sueño REM (TCR). El signo cardinal del TCR es REM sin atonía (RSA) que se extrae del electromiograma (EMG) obtenido mediante video-polisomnografía (v-PSG). Proponemos un método de cuantificación automática de eventos motores mediante el análisis de la envolvente del EMG en pacientes portadores del síndrome de microdeleción 22q11.2 (MD22q11), condición probablemente asociada a Enfermedad de Parkinson precoz. Material y método: Se etapificó 10 v-PSG domiciliarias mediante criterios estándar (AASM). Las épocas de sueño REM fueron analizadas visualmente en mini-épocas de 3 segundos para diagnóstico de RSA basado en el análisis de músculos mentonianos y flexor digitorum superficialis de ambos brazos (protocolo SINBAR) . Se contrastó el diagnóstico visual de eventos motores con la detección automática basada en el análisis de la envolvente (amplitud y coeficiente de variación, CVE) del EMG de cada músculo. Resultados: Los pacientes no presentaron RSA. Se obtuvo una reproducibilidad de detección visual vs. automática (Índice Kappa Cohen, IKC), de 0.798 (mediana de 10 casos). El parámetro crítico para la detección de eventos motores fue el CVE con una sensiblidad y especificidad de 0,887 y 0,968 para CVE>2. Conclusiones: El análisis de envolvente del EMG tiene una precisión buena a muy buena en la detección de eventos motores de significación clínica. Financiado por Proyecto Fondecyt 1171014 y Fundación Guillermo Puelma. Fondecyt: 1171014, Fundación Guillermo Puelma Keywords (1) Trastorno conductual del REM, (2) REM sin atonía, (3) Síndrome microdeleción 22q.

Functional genomics and morphological analyses demonstrate alterations in the cerebral cortical intrauterine development when exposed to a high-fat diet and omega-3 supplementation (Los análisis genómico funcional y morfológico demuestran alteraciones en el desarrollo intrauterino de la corteza cerebral ante una dieta alta en grasa y la suplementación con omega-3)

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La obesidad materna y la dieta alta en grasa se relacionan con un mayor riesgo de alteraciones neurológicas en la descendencia. A su vez, se ha demostrado que la suplementación con omega-3 mejora el desarrollo cognitivo. Para analizar el efecto de una dieta obesogénica y la suplementación con omega-3 sobre el desarrollo de la corteza cerebral se analizó la expresión de redes transcripcionales proinflamatorias, neurogénicas y de neurodiferenciación y se estudió la distribución morfológica de los compartimentos que participan en el desarrollo cortical. El análisis bioinformático se ejecutó con una base transcriptómica de corteza cerebral de ratones C57BL/6J alimentados durante 5 meses a partir del destete con una dieta obesogénica suplementada con aceite de pescado. El análisis morfológico se realizó en ratones C57BL/6J expuestos intrauterinamente a una dieta alta en grasa, suplementada con omega-3 (DHA) y sus controles (dieta normal con o sin suplementación con DHA). Nuestros resultados sugieren que la suplementación con omega-3 incide en redes genómicas funcionales similares a las afectadas por obesidad. Además, predice una alteración de procesos de sinaptogénesis y migración neuronal. Consistentemente se observó una disminución de los compartimentos proliferativos corticales en grupos alimentados con dieta alta grasa y aquellos suplementados con DHA, o DHA solo, en comparación a los alimentados con dieta normal ($p<0.05$). También se observó un aumento de la placa cortical inducido por DHA ($p<0.05$). Es posible que ambos: dieta alta en grasa y omega-3, reduzcan la proliferación neuronal, y que la administración de omega-3 aumente la velocidad proliferativa y migratoria neuronal.

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Obesidad, Desarrollo corteza cerebral, Omega-3

ORAL COMUNICATIONS II

Peripheral inflammatory biomarkers and ApoE genotype as risk factors of cognitive impairment in the Chilean GERO cohort: Preliminary study (Biomarcadores inflamatorios periféricos y genotipo ApoE como factores de riesgo de deterioro cognitivo en la cohorte chilena GERO: Estudio preliminar)

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We aim to study and correlate the inflammatory biomarkers, ApoE genotype with different cognitive domains in the GERO cohort (49 subjective complaint (SC) and 62 mild cognitive impairment (MCI), >70 years) and 33 healthy controls (HC). Plasma inflammatory proteins IL-2, IL-6, IL-10, TNF-α, CRP, SAP and ApoE genotype were analyzed and correlated with neuropsychological assessment. CRP showed a decreased expression in the SC compared to MCI and HC. SAP showed a decreased expression in SC as well as MCI compared to HC. A correlation of CRP with memory and social cognition in the SC and with memory in the MCI was found. SAP correlations were observed with nomination and repetition in the SC and with repetition in the MCI. Additionally, ApoE analysis was performed in 3 genotype groups: e2 (ε2/ε2- ε2/ε3, n=10), e3 (ε3/ε3, n=83) and e4 (ε2/ε4-ε3/ε4-ε4/ε4, n=20). Differences between SC and MCI were found in the e2 allele in social cognition. In the e3 allele in attention, executive function, memory, verbal fluency, language, social cognition and visuoconstructive skills. In the e4 allele in executive function, language, emotional recognition and functionality. SAP and CRP showed correlations with memory, language and social cognition, suggesting that these proteins may be associated with pathological aging. The ApoE e3 allele, the MCI showed an increased cognitive impairment compared with the e2 and e4 alleles, which can not be explained by the ApoE effect. The e4 allele, the MCI was observed to have an increased cognitive and functionality impairment.

FONDAP program 15150012/ANID-USA REDI170583
Keywords (1) Cognitive impairment, (2) Inflammatory biomarkers, (3) ApoE genotype.

Relación entre neurocognición, síntomas clínicos y pausas en el discurso en Esquizofrenia
Relationship between neurocognition, clinical symptoms and pauses in speech in Schizophrenia

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El presente estudio tuvo como objetivo establecer si existe correlación entre las pausas no comunicativas en el discurso de pacientes con diagnóstico de esquizofrenia y los síntomas positivos, negativos y cognitivos. Se realizaron entrevistas audiograbadas a 7 participantes con diagnóstico de esquizofrenia, las cuales fueron analizadas para medir cantidad y longitud de pausas no comunicativas. Los datos lingüísticos se correlacionaron con resultados en la escala PANSS de síntomas clínicos y el test MoCa para síntomas cognitivos. Todos los participantes realizaron pausas no comunicativas, las cuales se correlacionaron significativamente con síntomas positivos. Se encontró correlación positiva entre las pausas no comunicativas y tareas de memoria y visuoespacial y correlación negativa entre la tarea de atención y las pausas no comunicativas. Proyecto Fondecyt 11191122 Keywords (1) Esquizofrenia, (2) pausas, (3) discurso.

La Relación entre Actividad Cortical Asíncrona y los Potenciales de Campo en Atención The Relation between Cortical Asynchronous Activity and Field Potentials in Attention

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Spontaneous fluctuations occur at different spatial and temporal scales in the brain. Depending on its scale, these fluctuations can show characteristic hallmarks. For example, from a micro perspective, in spontaneous conditions cortical neurons fire action potentials in a seemingly stochastic manner, which extrapolated to an entire population shows a dynamical state that has been coined as the asynchronous irregular state (Brunel et al., 2000). Interestingly, when there is a local population of balanced excitation and inhibition recurrently connected, the asynchronous population generates a baseline of stochastic perturbation over the neuron's membrane potential of that local population (Destexhe et al., 2003). These perturbations have been proposed as optimal for information computation (Zerlaut and Destexhe, 2017) and at the behavioral level are associated with different states of attention (Reimer et al., 2014). Specifically, catecholaminergic modulation -which regulates brain states- is highly implicated in neuropsychiatric disorders and affects cognition, which has been implicated in the modulation of asynchronous activity (Pfeffer et al., 2018). Here we will explore the hypothesis of attentional modulation of local electrophysiological asynchronicity through catecholaminergic neuromodulation, analyzing novel electrophysiological markers such as 1/f slope of the power spectrum and Lempel-Ziv complexity as a proxy of asynchronous state. We will explore these measures and show how the complexity of the electrophysiological signals depends on excitation-inhibition balance of local cortical activity. Finally, we will show how this complexity fluctuates in attention and is tracked by pupil diameter fluctuations -a proxy of catecholaminergic modulation- in a visuospatial working memory task in humans.

Beca ANID Doctorado Nacional N° 21180871 Keywords (1) iEEG, (2) 1/f, (3) Cortical States.

Teaching with the Brain in Mind: Cognitive and Neural Correlates of Teaching (Enseñando con el cerebro en mente: correlato cognitivo y neuronal de la habilidad de enseñar.)

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Enseñar es una habilidad cognitiva compleja fundamental para el desarrollo de sociedades y culturas. Interesantemente, se ha documentado que esta habilidad también se presenta en otras especies (como chimpancés, aves, grandes felinos e incluso hormigas), lo cual revela su alto valor adaptativo. En términos generales, enseñar es una forma de altruismo, fundada en una motivación por ayudar, en la cual individuos donan sus conocimientos a otros para su uso. A pesar de su importancia, esta capacidad ha recibido relativamente poca atención desde las neurociencia cognitiva, de modo que la dinámica cerebral que la soporta es en gran parte desconocida. Recientes hallazgos derivados de estudios conductuales, de neuroimagen e hyperscanning han ido dando pistas acerca de la importancia de operaciones cognitivas como la teoría de la mente, las funciones ejecutivas y la metacognición durante el acto de enseñar. El objetivo principal de esta charla es presentar los potenciales marcadores neuronales y cognitivos que sustentan la habilidad de enseñar, articulando esta evidencia en un modelo neurocognitivo susceptible de ser testeado empíricamente.

FONDECYT 1201443 Keywords (1) Teaching, (2) Brain, (3) Cognition.

Spinal Cord Stimulation (SCS): A beneficial alternative for the treatment of motor symptoms of Parkinson's disease in the shortand long-term

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Introduction. Parkinson's Disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra (SN) and the presence of Lewy bodies. αsynuclein (α-syn) is the main component of Lewy bodies in sporadic cases of PD. Spinal Cord Stimulation (SCS), a neuromodulation technique consisting in the epidural delivery of electrical pulses in the dorsal spinal cord, has emerged as a potential treatment for the motor symptoms of PD. Evidence collected in neurotoxic PD model suggest that SCS could have long-term effects associated to neuroprotection and neuroplasticity. We study the possible neuroadaptations induced by SCS to improvement the motor function in an α-synuclein model of PD. Material and Methods. Sprague Dawley male rats were injected unilaterally in the SN with AAV6-WT-α-syn. Thirtytwo days after the viral injection, they were treated with highfrequency (300 Hz) SCS for ten weeks, two sessions/week. We evaluated the motor performance by Stepping Test, the density of dopaminergic axons by immunohistochemistry and the signaling pathways modulated by SCS with RNAseq. Results. SCS prevents the motor alteration in α-syn model, without affect the nigrostriatal pathway. In the SN, SCS induces the modulation of genes expression involved in cellular and molecular mechanisms associated to neuroplasticity, such as: angiogenesis, axon guidance and signaling through G protein-coupled receptors (ex. dopamine 2 receptor), etc. Discussion. These results suggest that SCS might exert neuroplastic effects in the nigrostriatal pathway, contributing to alleviate the motor symptoms in a PD model. Fondecyt-1151478, FONDAP-15150012, Millennium Scientific Initiative-P09-015-F, Fondecyt-1191497//1191003, Beca Doctorado Nacional-21181114. Keywords (1) Parkinson's Disease – Therapeutic strategy – Spinal cord stimulation.

Análisis automático en español, identifica y predice la esquizofrenia. Spanish automatic language analysis identifies and predicts Schizophrenia.

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Introducción. La esquizofrenia (EQZ) se considera un grave trastorno psiquiátrico. Actualmente, no se han informado biomarcadores clínicos para esta enfermedad, pero varios estudios han demostrado la utilidad potencial del análisis del lenguaje automatizado para mejorar la precisión del diagnóstico en pacientes psicóticos de habla inglesa. Objetivo. Proponemos biomarcadores lingüísticos para EQZ, mediante análisis automatizado en hispanohablantes. Metodología. Analizamos 30 características del lenguaje (4 medidas de fluidez verbal, 6 léxicas- semánticas, basado en la coherencia de la oración y 20 características de Productividad Verbal) en 135 pacientes hispanohablantes de 3 grupos: controles sanos (n = 49), primer episodio de psicosis (n = 47) y sujetos con EQZ crónica (n = 39). Propusimos 2 predictores automáticos de EQZ para: (i) identificar a los pacientes esquizofrénicos hispanohablantes de los controles sanos, y (ii) predecir la aparición de esquizofrenia en pacientes con un primer episodio psicótico. Resultados. De 30 características del lenguaje evaluadas, 20 de ellas mostraron diferencias estadísticas dentro de al menos dos grupos de pacientes. Utilizando las 10 principales características del lenguaje descorrelacionado, propusimos un clasificador de control automatizado para EQZ que logra un 86% de precisión utilizando una metodología de Random Forest. Además, utilizando las 10 principales variables descorrelacionadas clasificadas, más los datos demográficos, propusimos un predictor automatizado de aparición de EQZ para pacientes con un primer episodio psicótico, con una precisión de predicción del 67%, similar a PANSS Scale. PROYECTO FONDECYT INICIACIÓN 11191122 Keywords (1) esquizofenia, (2) lenguaje automatizado, (3) predicción de psicosis.

POSTER SESSION I

Two Conserved Alpha Helix In Corticotrophin Releasing factor Binding Protein Serves as Sorting Signals to the Regulated Secretory Pathway

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Corticotrophin releasing factor binding protein (CRFBP) binds CRF with high affinity. CRF is a key player in the stress response activating the hypothalamic pituitary adrenal axis. CRFBP has been thought as an inhibitory protein controlling plasmatic CRF levels during human pregnancy. Recently it has been proposed that CRF-BP could also facilitate the activation of CRF-R2 receptor in the central nervous system. CRFBP enters the regulated secretory pathway for its release. However, the destination signals leading CRF-BP to regulated secretory granules (RSG) is unknown. We modeled the protein structure of CRFBP and its alpha projection (PEPWHEEL) together with studies of heterologous transfection of chimeras over-expressed in PC12 cells. Modeling of the protein showed the presence of three alpha-helix domains (50-74, 128- 149 and 229-251). Domains “50-74 and 229-251” of CRFBP are highly conserved among mammalian species and have a hydrophobic patch characteristic of other destination domains to RSG. The results showed that the alpha-helix domain “50-74” of CRFBP is capable of restore the destination of a chimeric variant of proCART precursor, without its sorting domain to the RSG. Furthermore, the presence of the alpha-helix domain (50-74)-CRFBP in the variant chimeric proCART allowed its secretion triggered by a depolarizing stimulus. Preliminary data showed that the “229- 251” domain attached to the chimeric variant proCART is also secreted by a stimulus. We plan to complete the data carrying out colocalization studies to the RSG for the “229-251” domain to show that both “50-74” and “229-251” domains of CRFBP are essential for its destination to RSG. Fondecyt 1191274 Keywords (1) CRFBP Corticotrophin releasing factor binding protein, (2) RSG Regulated Secretory Granules.

Circadian control of synaptic connectivity and neuropeptide release during Drosophila metamorphosis.

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In Drosophila melanogaster, the emergence of adult fly is controlled by the circadian clock, which restricts the time of emergence to a specific window of time. This gating of emergence depends on the activity of the central circadian pacemaker in the brain and of a peripheral clock located in the prothoracic gland (PG). We have recently shown that central brain clock neurons communicate with the PG clock by transmitting time information to peptidergic neurons that produce the neuropeptide, PTTH, and that these neurons in turn communicate with the PG via the PTTH neuropeptide. However, the cellular mechanism by which PTTH neurons transmits the time information to the PG is currently unknown. We employed a genetically encoded calcium sensor and demonstrate that calcium levels in PTTH neurons oscillate under circadian control. In addition, by the use of immunofluorescence we observed daily changes in the levels of PTTH present in the terminals of the PTTH neurons in the PG. Furthermore, using genetic manipulations we showed that a pathway -independent of PTTH signaling- mediated by protein G in PG regulates the period of adult emergence. Establishing how PTTH signaling affects the PG clock during adult emergence could serve as a paradigm to understand how daily steroidal glucocorticoid hormone rhythms are generated in mammals. FONDECYT-1180403. Instituto Milenio Centro Interdisciplinario de Neurociencia de Valparaíso. CONICYT Doctoral Fellowship- 21180133 Keywords (1) circadian rhythm, (2) neuropeptide, (3) drosophila.

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

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Introduction: Small fiber neuropathy (SFN) is a disorder in which only the small sensory cutaneous nerves are affected characterized by degeneration of the distal terminations of small fiber nerve endings and fail to regenerate. Evidence suggest that axonal degeneration is an early event in the neuropathy onset, and reduction in target-derived trophic expression has been poorly investigated in the pathogenesis of SFN. Small fibers are located close to skin cells, these skin cells are known to produce axon guidance factors, modulating nerve fiber elongation and regeneration. Skin cells produce neurotrophic factors enabling a precise control of cutaneous innervation. Methods: Expression levels of neurotrophic factors and its receptors in human skin biopsy from patients with SFN were examined by qRT-PCR. Also, were used for culture of keratinocytes and wounding to induce the secretion of neurotrophic factors. DRGs were exposed to keratinocyte conditioned medium to assess neurite outgrowth and, the cell-conditioned medium was analyzed via ELISA. Results: We found that in patients with SFN expression of neurotrophic factors mRNA levels was significantly reduced, particularly NGF and GDNF. The expression of their receptors did not change. DRG treated with SFN keratinocytes-conditioned medium decreased their neurite outgrowth compared with healthy keratinocytes. Furthermore, we demonstrate that mediators released induce reduced neurite outgrowth due to diminished NGF and GDNF protein levels. Discussion: Our results demonstrate the impact of epidermal keratinocytes on skin innervation and emphasize the role as key players of skin cells-produced neurotrophic factors, as well as reduction in target-derived trophic expression in small fiber neuropathy FONDECYT-1161019 Keywords (1) Small Fiber Neuropathy, (2) Sensory, (3) Trophic factor.

General characterization between mouse primary culture of trigeminal and dorsal root ganglia neurons

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Primary sensory neurons, whose somata are located in dorsal root ganglia (DRG) and in trigeminal ganglia (TG), transduce environmental stimuli from body and head, respectively, further transmitted to the CNS. High specialization of these neurons is correlated with their great heterogeneity, although this is not fully understood in cultures of isolated neurons. In order to compare some general features of in vitro models routinely used in pain studies, we performed primary cultures of adult mouse DRG and TG neurons. Using immunostaining, we found sensory neurons (βIII-tubulin+) which were classified according to somata size diameter as small (25 µm). Medium-size neurons was the largest subpopulation in cultures, and the small subpopulation was higher in TG as compared to DRG cultures. Since ion channels expression represents valuable information to classify sensory neurons, we found purinergic receptors P2X2R and P2X3R predominantly expressed in medium–size neurons from TG and DRG cultures. Additionally, P2X3R+ neurons were more abundant than P2X2R+ neurons in medium–size neurons from TG culture. TRPV1 expression was found in small- and medium-size neurons, and unlike P2X2R/P2X3R, it was absent in large neurons. Finally, in our primary culture we found several non-neuronal cells such as satellite glial cells (glutamine synthetase+), fibroblasts (vimentin+), Schwann cell (MBP+) and macrophages (Iba1+). Our preliminary in vitro analysis reflects some differences between TG and DRG neurons, possibly supporting previous findings related to expression pattern and functions between TG and DRG neurons. Supported by FONDECYT 1191552, ENL20/18, and Millennium Nucleus for Study of Pain (MiNuSPain) Keywords (1) TG, (2) DRG, (3) Sensory neurons.

Microtubule polyglutamylation controls neurites growing in mice hippocampal neurons. Microtubule polyglutamylation controls neurites growing in mice hippocampal neurons.

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In neurons, microtubules are essential for intracellular transport, organelle positioning and neuronal polarization. The tail domains located at the C-terminal of α and βtubulin are the targets for several posttranslational modifications (PTMs) of tubulin, such as tyrosination/detyrosination and polyglutamylation. These PTMs might confer different functional properties to microtubules by modulating for instance the binding of selected microtubule associated proteins (MAPs). Here, we investigate the reciprocal control of tubulin PTMs by MAPs. Polyglutamylation is one of the most abundant tubulin-PTM in neurons which is catalyzed by a family of tubulin tyrosine ligase-like (TTLL) enzymes. Overexpression of different polyglutamylases in early stages of in vitro neuronal cultures impairs neuronal polarization, decrease neurite lengths and an importantly impairs mitochondria axonal traffic. Consequently, loss of function of neuronal TTLLs induced an increase in neurite elongation OR axon elongation. Considering the importance of a precise control of polyglutamylation levels in neurons, we investigated potential molecular mechanisms that regulate TTLLs. We describe that the TTLL1 enzyme directly interact with the microtubule-associated protein MAP1B. Loss of function of MAP1B leads to increased polyglutamylation of α-tubulin in mice brain. At the cellular level, neurons lacking MAP1B display shorter neurites along with reduced rate of mitochondria movement, showing a similar phenotype seen in overexpression of TTLLs. Altogether our findings suggest that MAP1B could participate in the regulation of enzymes involved in the generation of PTMs on microtubules and propose a novel layer of regulation where MAPs might control the activity of the enzymes that control microtubule post-translational modifications. Supported by FONDAP 15150012 and FONDECYT 1180419 (to CGB) and CONICYTPFCHA 21150824. Keywords (1) Microtubule, (2) Neuron polarization, (3) Polyglutamylation.

Calcium release from the endoplasmic reticulum contributes to ferroptotic cell death in primary hippocampal neurons (La liberación de calcio desde el retículo endoplá smico contribuye a la muerte celular ferroptótica en neuronas primarias del hipocampo)

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Introduction: Neuronal calcium signaling plays a crucial role in diverse physiological responses, including neuronal survival, neurotransmitter secretion and synaptic plasticity, among others. Deregulated calcium signals, however, lead to neuronal death. Ferroptotic cell death, characterized by iron-dependent lipid peroxidation, intracellular glutathione depletion and altered mitochondrial morphology, has gained recently increased importance due to its implication in diverse neurological disorders. Inhibition of glutathione peroxidase 4 (Gpx4), a key antioxidant enzyme that reverses lipid peroxidation, promotes ferroptosis in some cell types, albeit no information is available regarding ferroptosis in primary hippocampal neurons. Moreover, the role of calcium signaling in ferroptosis, and in particular the contribution of calcium release from the endoplasmic reticulum (ER), have not been reported Hypothesis: Calcium release from the ER mediated by ryanodine receptor (RyR) channels contributes to ferroptosis in primary hippocampal neurons of the rat. Methodology: Primary hippocampal cultures enriched in neuronal cells were incubated with RSL3, a selective Gpx4 inhibitor, in the presence or absence of 20 µM ryanodine, a concentration that suppresses RyR activity. Metabolic cell viability was determined by the MTT assay. Results: Incubation with RSL3 (30 µM) for 24 hours reduced metabolic viability by approximately 50%; cells previously incubated with ryanodine displayed less reduction of metabolic viability but exhibited lower values than the controls. Conclusion: Hippocampal neurons in culture are susceptible to ferroptosis and RyRmediated calcium release partially contributes to this type of cell death, which appears to occur in some neurodegenerative diseases. Support: ICN09_015; BMBF180051; Agencia Nacional de Investigación y Desarrollo (ANID)/ Programa de Doctorado en Ciencias Biomédicas CHILE/2020 - 21200346 Keywords (1) Ferroptosis, (2) Calcium, (3) Hippocampus.

Temperature sensitivity in the TRPM8 channel is harbored at the C-terminal domain Temperature sensitivity in the TRPM8 channel is harbored at the C-terminal domain

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The TRPM8 channel has been unequivocally demonstrated as a cold sensing TRP channel. We recently proposed that a folding reaction of the C-terminal end -that encloses a coiled coil domain- drives temperature-dependent gating in TRPM8. To further explore the role of C-terminal domain in temperature sensitivity, we constructed chimeric channels between TRPM7 (temperature insensitive) and TRPM8 (cold sensitive), by exchanging their coiled-coil domains. Electrical recordings in X. laevis oocytes revealed that the chimera TRPM8ccTRPM7 (TRPM8 harboring the coiledcoil domain of TRPM7) obliterated temperature sensing, whilst the converse chimera TRPM7ccTRPM8 acquired the ability to sense cold. Using anisotropic thermal diffusion (ATD) analysis, we identify residues located in the coiled-coil domain, involved in thermal propagation and used site-directed mutagenesis to neutralize them by alanine and performed electrophysiological recordings of the mutant channels expressed in X. laevis oocytes. The analysis rendered two temperature-insensitive mutants (TRPM8R1079A and TRPM8D1086A). Molecular dynamics simulations (540 ns) at 278K and 320K, shows that compared to wild type channel, these two mutants affect the volume occupancy in the C-terminus domain, associated with structural changes in the coiled-coil region. Our analysis show that the C-terminal domain of the TRPM7 channel is mostly hydrophobic, while the TRPM8 is conformed by neutral, polar, and hydrophobic amino acids, and exhibit different degree of disorder disposition of their residues. Thus, we propose that temperature sensing of TRPM8 channel arises from a finely tuned amino acid composition that enable cold-driven rearrangements of the C-terminus domain that trigger channel activation. This work is supported by: FONDECYT 190203 (to R.L.), 1170733 (to F.G.-N.), 1180999 (to K.C.) and 3170599 (to I.D-F). PAI7719087 (to I.D.-F.); US Army Research Office Cooperative Agreement W911NF-17-2-0081 (to F.G.-N.). The Centro Interdisciplinario de Neurociencias de Valparaiso (CINV) is a Millennium Institute (ICM-ANID), Project P09-022-F. Keywords (1) Transient Receptor Potential Melastatin type 8 channel, (2) Temperature sensor.

Formation of heteromeric channels by cx26s17f syndromic deafness mutant and cx30 and its consequences on cochlear pathology formation of heteromeric channels by cx26s17f syndromic deafness mutant and cx30 and its consequences on cochlear pathology

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Specific mutations in connexin 26 (Cx26) gene produce syndromic deafness, like Keratitis-Ichthyosis-Deafness, where patients develop deafness and skin disease. Cx26 forms hemichannels (HC) and gap junction channel (GJC) that that interconnects intracellular with extracellular environments and adjacent cytoplasms of two neighboring cells, respectively. Cx26 is co-expressed with Cx30 in keratinocytes in the skin, and in the supporting cells (SC) of the organ of Corti (OC) in the cochlea. One KID mutation found in patients is Cx26S17F. It was unknown if Cx26S17F can form heteromeric channels with Cx30. By using exogenous expression system, biochemical, eletrophysiological and fluorescent imaging methods we found that Cx26S17F and Cx30 form heteromeric non-functional GJCs but hyperactive HCs. This deafness-associated heteromeric HCs do not respond to HC blocker La3+ and are less sensitive to [Ca2+] e, remaining open at a physiological [Ca2+]e that normally close wild type HCs. Consequently, cells that express Cx26S17F/Cx30 HCs present higher [Ca2+]i concentration, and increased cell damage and death. Remarkably, ex vivo expression of conditional knock-in Cx26S17F in cochlear explants of transgenic mouse changes the distribution of Cx26 and Cx30 in SC of the OC to more intracellular localization. These cells also present smaller GJ plaques and hyperactive HCs that do not respond to [Ca2+]e or to the HC blocker carbenoxolone. Moreover, expression of Cx26S17F produces damage of hair cell stereocilia, where sound mechanoreceptors are located, suggesting that it cause excitotoxic environment in the OC. To our knowledge, this is the first study of cochlear Cxs using a mouse model of syndromic deafness. PhD fellowship (FIB-UV), ANID (scholarship 21150585) and Bridge scholarship (CINV) (to AA). FONDECYT (ANID) grant 1171240 and ICN09-022-F (ICM-ANID, CINV) (to ADM). Centro Interdisciplinario de Neurociencia de Valparaíso (CINV) is a Millennium Institute supported by the Millennium Scientific Initiative of the Ministerio de Ciencia, Tecnología, Conocimiento e Innovación de Chile. Keywords (1) connexin, (2) deafness.

Glycine Receptor Inhibition Differentially Affect Selected Neuronal Populations of the Developing Embryonic Cortex, as Evidenced by the Analysis of Spontaneous Calcium Oscillations (La inhibición del receptor de glicina afecta diferencialmente a poblaciones neuronales de la corteza embrionaria en desarrollo, lo que se evidencia por el análisis de las oscilaciones espontáneas de calcio).

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The embryonic developing cerebral cortex is characterized by the presence of distinctive cell types such as progenitor pools, immature projection neurons and interneurons. Each of these cell types is diverse on itself, but they all take part of the developmental process responding to intrinsic and extrinsic cues that can affect their calcium oscillations. Importantly, calcium activity is crucial for controlling cellular events linked to cell cycle progression, cell fate determination, specification, cell positioning, morphological development and maturation. Therefore, in this work we measured calcium activity in control conditions and in response to neurotransmitter inhibition. Different data analysis methods were applied over the experimental measurements including statistical methods entropy and fractal calculations, and spectral and principal component analyses. We found that developing projection neurons are differentially affected by classic inhibitory neurotransmission as a cell type and at different places compared to migrating interneurons, which are also heterogeneous in their response to neurotransmitter inhibition. This reveals important insights into the developmental role of neurotransmitters and calcium oscillations in the forming brain cortex. Moreover, we present an improved analysis proposing a Gini coefficient-based inequality distribution and principal component analysis as mathematical tools for understanding the earliest patterns of brain activity. Este trabajo fue financiado por el proyecto “CONICYT, PAI, convocatoria nacional subvención a instalación en la academia, convocatoria año 2018”, grant number: PAI77180086 otorgado al investigador principal, Dr. Ariel Ávila. Keywords (1) Cortex, (2) Development, (3) Glycine receptor.

(Intermittent ketogenic diet improves hippocampal synaptic plasticity in aged mice (La dieta cetogénica intermitente mejora la plasticidad sináptica del hipocampo en ratones envejecidos)

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Physiological aging is a natural process, which at the brain level is associated with cellular and functional deterioration that precedes a decline in learning and memory, mainly in the hippocampus. Sedentary lifestyles and an excess of carbohydrates and saturated fats induce a dysregulated metabolism, inducing a deterioration in hippocampal synaptic plasticity during age. On the other hand, lifestyles that include bioenergetic challenges such as exercise or fasting favor β-oxidation to produce ketone bodies that increase the expression of BDNF. In aging, antecedents show an vulnerability in the function and structure of the synapse, which translates in the decrease number of glutamatergic receptors. Recent studies show that an intermittent ketogenic diet increases memory in aging animals. The link between energy metabolism and neuronal signaling suggests that metabolic interventions could enhance synaptic plasticity in aging. Here, we propose that an intermittent ketogenic diet improves synaptic plasticity by inserting new AMPA receptors in the plasma membrane mediated by changes in their phosphorylation levels in serine 831. We found that hippocampal LTP show a decrease in slices of aged rats. Using synaptosomal preparations combined with western blotting of the CA1 area of aged mice we found a decrease in phosphorylation in the serine residue 831 in hippocampus. Such phosphorylation was reversed when animals were administered with a ketogenic diet. These results help us to understand the effect of an intermittent ketogenic diet on the in the synaptic plasticity during aging, thus providing a molecular indication of the effects of aging on cognitive function. This work was supported by FONDAP 15150012. Keywords (1) Hippocampus, (2) Synaptic plasticity, (3) aging.

Wistar Structural alterations in the hippocampus associated to prenatal and one-year arsenic exposure in Wistar rats) Alteraciones estructurales en el hipocampo asociadas a la exposición prenatal y durante un año al arsénico en ratas

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Compelling evidence points to the critical role of perinatal insults leading to brain structural abnormalities as an important risk factor for disease. It is widely recognized that exposure to arsenic (iAs) produces deleterious effects in the brain. Worldwide population-based studies demonstrate that iAs-exposure is inversely associated with cognitive function among children. At cellular level, iAs affects energy generation, neurotransmitters, and promotes the generation of ROS. Accordingly, iAs favors molecular changes resembling the functional and pathologic features of neurodegeneration. To investigate the long-term effects of iAs on the structure and myelination of the hippocampus, we undertook a longitudinal study with repeated follow-up assessments in Wistar rats. Animals were divided into 1) without arsenic and 2) iAs in drinking water. Animals received the treatment from gestation, through the dams, and continued until 2, 4, 6, 12 months. The microstructure in vivo was analyzed by means of MRI at the same ages. In parallel, animals were sacrificed for immunohistochemical staining of myelin, synaptophysin (SYP) and GFAP. Ultrastructural imaging demonstrated that iAs altered the distribution and orientation of white matter fibers. This was accompanied by significant myelin loss in CA1 at 12 months and in CA3 at 6-12 months. A remarkable change in astrocytes morphology was evidenced and increased GFAP immunopositivity at all ages. SYP positivity only presented a significant increase in CA3 at 2 months by iAs as compared to controls. These results demonstrate a significant and persistent impact on hippocampus development that may underlie the reported cognitive deficits under environmental pollution. This research was supported by CONACYT (241009) for S.Z. and fellowship 503319 for S.A.N. Keywords (1) Neurodegeneration, (2) Astrocyte, (3) Arsenic.

Chronic Pannexin 1 blockade improves cognitive performance in the APP/PS1 mice model of Alzheimer`s disease (La administración crónica de probenecid bloquea los canales de Panexina 1 y mejora el desempeño cognitivo en un model de la enfernedad de Alzheimer.)

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Synaptic loss induced by soluble oligomeric forms of the amyloid β peptide (sAβos) is one of the earliest events in Alzheimer´s disease (AD) and is thought to be the major cause of the cognitive deficits. Pannexin 1 (Panx1), a membrane protein implicated in cell communication and intracellular signaling, modulate the induction of excitatory synaptic plasticity under physiological contexts and contribute to neuronal death under inflammatory conditions. Probenecid is an FDA approved drug formerly used for gout treatment, and currently reported as a Panx1 blocker. Previously we reported that in vitro treatment of brain slices from 6 months old (mo) APP/PS1 mice with 100uM of Probenecid (PBN) mitigates synaptic plasticity defects. To find a time window for an effective probenecid treatment, we evaluate chronic administration of PBN in 18, 12, and 3 mo APP/PS1 mice. Using a battery of behavioral paradigms, we assessed the effect of PBN on the cognitive function along with histopathological markers, and structural and functional plasticity. We found that chronic PBN administration improved spatial memory in 12 and 18 mo APP/PS1 mice while does not have effects on synaptic plasticity deficits, amyloid-beta plaques, or reactive gliosis. Surprisingly, we observed that PBN increased dendritic arborization in both WT and APP/PS1 mice, suggesting that Panx1 blockade promotes dendritic remodeling of the neuronal cytoskeleton. Our results suggest that Panx1 blockade with PBN could interfere with toxic signaling leading to memory and plasticity impairments. This work was supported by Doctoral ANID fellowship grant #21190247 and Fondecyt grant #1201342 (A.O.A), Millennium Institute CINV (ICM MINECOM P09-022F). Keywords (1) Azheimer’s disease, (2) Pannexin 1, (3) Synaptic plasticity.

Contribution of Kv1.6 channels to neuropathic pain modulation in vivo and modulation of spontaneous activity on damaged sensory myelinated axons in vitro (Contribución de canales Kv1.6 a la modulación del dolor neuropático in vivo y a la modulación de la actividad espontánea en axones sensoriales mielinizados in vitro.)

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Neuropathic pain following peripheral nerve injury is associated with hyperexcitability in damaged myelinated sensory axons, which partially normalizes overtime. Belatedly following nerve injury, axonal Kv1 channels switch the expression of its α-subunits, downregulating Kv1.1 and 1.2, and overexpressing Kv1.6. This coincides with a marked reduction in exacerbated spontaneous activity in injured spinal nerves, and diminished mechanical pain behavior. Blocking Kv1 channels with α-DTX reinstates damaged-triggered hyperexcitability. Aim: to further investigate Kv1.6 involvement in dampening hyperexcitability following severe sensory axon damage. We determined mechanical allodynia(MA) in a sciatic nerve neuroma model in adult Sprague Dawley male rats. MA was evaluated by paw-withdrawal assay for up to 5weeks after surgery in the presence or absence of 30µM CPY-Fe1 (conopeptide Kv1.6 blocker). We cultured embryonic rat DRG explants in myelinating conditions. Spontaneous and 30mM KCl-evoked activity was recorded in axons in control conditions or with 30µM CPY-Fe1. Rats developed MA after surgery, which recovered overtime. CPY-Fe1 treatment abolished this recovery. Undamaged DRG cell cultures express Kv1.2 at paranodes and juxtaparanodes; following axotomy Kv1.6 was expressed. Ca2+ influx was induced by KCl stimuli, both before and after axotomy. Action currents(AC) under voltage-clamp axon-attached mode occur at a rate of 1.6 AC/min on single undamaged axons(n=9). KCl stimulation increases this up to 9.2 AC/min($p=0.0313$;n=6). Acutely after axotomy, basal firing rate rises to 5.5 AC/min($p<0.01$;n=5), which tends to normalize overtime. We are studying the effect of blocking Kv1.6 on axotomized axons and the use of lentiviral-mediated Kv1.6 overexpression on the electrical activity of DRG explant axons.
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Keywords
(1) Neuropathic Pain, (2) Kv1 Channels, (3) Spontaneous activity.

Keeping an eye on Pannexin-1: new target for age-related chronic inflammation? Keeping an eye on Pannexin-1: new target for age-related chronic inflammation?

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Ageing is a chronic degenerative process caused by multifactorial phenomena accumulated during life course. In the retina, decrease of photoreceptors and retinal ganglion cell numbers, detritus accumulation, and low-grade chronic inflammation has been reported. So far, Pannexin-1 (Panx1) channels have being related to the beginning and progression of several age related inflammatory conditions, such as Alzheimer's disease, glaucoma and age-related macular degeneration. Their opening leads to ATP release and neuronal cytotoxicity through purinergic and additional Panx1 activation; promoting increased intracellular Ca2+, membrane depolarization, caspase/inflammasome activation, and neuronal death. Although Panx1 is widely expressed along the retina, it is unknown if contributes to the neuronal deterioration associated to natural ageing. We evaluated Panx1 levels at different ages through western blot and immunofluorescence in mouse retina. For channel activity, dye uptake and calcium signals were evaluated in the presence of Panx1 inhibitors. Finally, inflammatory markers were evaluated in both wild type and Panx1 knock out (Panx1-/-) older mice. Interestingly, increased levels of Panx1 was detected in aged retinas (from 5 to 14- month old) compared to younger animals (1 and 2-month old). Consistently, aged retinas also presented higher dye uptake and impaired calcium signal respect younger retinas. Since in both cases responses were sensitive to Panx1 inhibitors, it suggests an increase of Panx1 channels activity. Conversely, our mouse model lacking Panx1 gene did not showed degenerative sings in aged retinas. Altogether, this data strongly suggests that Panx1 dysfunction in aged retinas could be contributing to inflammation and consequent changes in neuronal retina. Funding by Fondecyt Regular (1171240), Instituto Milenio CINV (P09-022F), Fondecyt Postdoctoral (3180149), and Fondecyt Postdoctoral (3200342). Keywords (1) Pannexin-1, (2) ageing, (3) inflammation.

Effect of blisters fluid from recessive dystrophic epidermolysis bullosa patients on axonal regeneration (Efecto del fluido ampollar de pacientes con epidermólisis bullosa distrófica sobre la regeneración axonal)

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Recessive dystrophic epidermolysis bullosa is a genetic skin condition that leads to extended blisters generation. Skin regenerates after blistering but epidermal reinnervation is not complete, leading to a secondary small fiber neuropathy that reduces quality of life of patients. We aimed to investigate if the content of the blisters of RDEB patients may influence intraepidermal fiber regeneration after lesion. We used rat dorsal root ganglia (DRG) explants to generate an in vitro axotomy model. When axons have grown radially from the cell bodies, we cut them and measured their growth three days after axotomy in vitro. We treated them with blisters' fluid of RDEB patients or with healthy volunteers' plasma as control. We observed a significant lower length in newly regenerated axons in DRGs treated with the fluid of blisters compared with DRG treated with healthy volunteers' plasma. The length of newly grown axons in cultures treated with 2.5% healthy plasma was 2415 ± 313.1 µM, while in cultures treated with 2.5% RDEB blister fluid was 1394 ± 154.4 µM (n=5). Axonal length in neurons treated with 5% healthy plasma was 2298 ± 429.0 µM, while in cultures treated with 5% RDEB blister fluid was 969.1 ± 111.1 µM (n=5). This work constitutes an initial step in elucidating the effect of the content of the RDEB's blisters on sensory neurons. We hypothesize that molecules in the blister´s fluid may be inhibiting axonal regrowth and blocking epidermal reinnervation after a skin injury, leading to a secondary small fiber neuropathy in RDEB.

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blister, epidermollysis bullosa, axon regeneration

Stress-Related Neuropathic Itch? Study of Pruritus and Axon Regeneration in Atopic Dermatitis Patients

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Itch is an unpleasant sensation signaled by C-fibers that triggers the desire to scratch. Atopic dermatitis (AD) is a skin condition characterized by intense pruritus that may be exacerbated by stress. Thus, we aimed to explore the differential influence of stress perception over the skin in 68 AD patients that self-reported stress being a trigger for itch or not (susceptible to stress, SS; non-susceptible to stress, NSS, respectively). Several characteristics of AD and skin physiology were evaluated. DRG explants were treated with patients' serum to analyze the axon regeneration after an axotomy.Mean age was 26±10 in SS (n=54) and 22±12 years in NSS (n=14). Frequency and intensity of symptoms were higher in SS than in NSS (SS 18±6 vs. NSS 12±6 days, $p<0.001$; SS 11±7 vs. NSS 5±4, $p<0.001$, respectively). SS patients had itchy skin every day during the previous week (SS 87%, NSS 40%, $p<0.001$) and remarkably, they also reported feeling pain. Severity was different (SS 47±18 vs. NSS 33±15, $p<0.01$), which was related to the percentage of lesioned skin (SS 15±18, NSS 6±7, $p<0.05$) and pruritus level (SS 7±2, NSS 4±2, $p<0.0001$), but not to eczema intensity. Skin physiological parameters were not different between groups. Finally, DRG explants treated with SS serum had significantly shorter neurites after an axotomy than explants treated with NSS serum.Itch differences among patients may be related to an amplification of skin sensitivity by abnormal C-fiber innervation modulated by stress, while the impairment in axon regeneration suggests alterations related to neuropathic itch.

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Stress, Itch, Axon

Altered secretion of astrocyte-derived extracellular vesicles contribute to the early metabolic failure in Huntington's disease. (Alterada secrecion de vesiculas extracelulares derivadas de astrocitos contribuye a la falla metabolica temprana en la enfermedad de Huntington).

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Huntington's disease (HD) is a neurodegenerative disorder caused by a glutamine expansion at the first exon of the huntingtin gene. Huntingtin protein (Htt) is ubiquitously expressed and it is localized in several organelles, including endosomes. HD has been associated with a failure in energy metabolism and oxidative damage. Ascorbic acid is a powerful antioxidant highly concentrated in the brain where acting as a messenger, modulating neuronal metabolism. During synaptic activity, ascorbic acid is released from glial intracellular reservoirs and it is taken up by neurons. Using an electrophysiological approach in YAC128 HD slices, we observe a decreased ascorbic acid flux from astrocytes to neurons, which is responsible for alterations in neuronal metabolic substrate preferences. Ascorbic acid efflux and recycling was decreased in cultured astrocytes from YAC128 HD mice without changes in the expression of proteins related to ascorbic acid homeostasis. We demonstrated that ascorbic acid is released from astrocytes through extracellular vesicles (EV). Decreased number of particles and the exosomal markers were observed in EV fractions obtained from YAC128 HD brain and cultured YAC128 HD astrocytes. We also observed a decrease in radioactive ascorbic acid content in EVs fractions obtained from cultured YAC128 HD astrocytes. Using electronic microscopy, we observed a decreased number of multivesicular bodies (MVBs) in the striatum of YAC128 HD mice. This support the idea that MVBs biogenesis is altered in presence of mutant Htt. Therefore, we suggest that a decrease in EV-mediated ascorbic release from astrocytes would be responsible for the early metabolic failure in HD.

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Huntington's disease, Ascorbic acid, extracellular vesicles

Role of basal forebrain in olfactory discrimination of complex mixtures

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The basal forebrain (BF) is one of the most important neuromodulatory nuclei in mammals, projecting a large part of the cortex and the olfactory system. It is involved in various cognitive processes such as attention, learning, memory and sensory discrimination.The olfactory system participates in fundamental behaviors such as the predator's identification and food localization. When the odorant molecules enter the nose, information is transmitted to the olfactory bulb. The neurons of this structure project their axons towards the piriform cortex, responsible for integrating information from odors and in the generation the olfactory perception. In olfactory coding, not only information from the external environment or "bottom up" is involved, but also information "top down" from the neuromodulatory nuclei. For example, the cholinergic and GABAergic fibers of the BF project their axons to the olfactory bulb and the piriform cortex, specifically from the horizontal limb of the diagonal band of Broca (HDB). However, the role of in vivo acetylcholine and GABA release from the HDB in the context of discrimination of odorants is still unknown.Here, to evaluate the role of HDB in olfactory discrimination we carried neuronal activation, through in vivo optogenetics, of neurons of this brain region in mice simultaneously with a behavioral go/no-go discrimination task of complex mixtures of odorants. We expressed channelrhodopsin-2 in HDB neurons and implanted an optical fiber in the area, to spatially and temporally control neuronal activation. Preliminary results indicate that activating HDB neurons facilitates olfactory discrimination of complex mixtures of odorants in rodents.

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olfactory coding, go-no go, optogenetics

A neural signal of temporal coordination as a mechanism of active sensing in rats (Una señal neuronal de coordinación temporal como mecanismo de la percepción activa en ratas)

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The perception of the environment by self-initiated movement requires precise sensorimotor coordination. The nature and features of this coordination are still unclear. Evidence shows modulation of local field potential in the primary visual cortex (V1) temporally locked to exploratory eye movements. It is unknown if this modulation contributes to sensorimotor coordination and if it is necessary or sufficient for the active sensing of the environment.Using rats trained in a selection task designed to assess animal control over the occurrence of visual stimuli, our work aims to artificially replicate V1 modulation during active sensing by electrical microstimulation with cortical electrodes. Here, we report a behavioral study of rats in this task and an analysis of the spectral features of V1 activity in rats to determine the stimulation time and frequency we will use in the next stage of this study.The performance of the animal in the task adequately discriminates self-initiated movement control over the occurrence of visual stimuli. V1 recordings show a significant increase in beta band power 100-150 ms before the execution of movement controlling the visual stimulus event. This finding is consistent with other reports showing increased beta activity in primary sensory cortices associated with motor actions.The electrical microstimulation of V1 with the retrieved time and frequency, coupled with visual stimuli not initiated by the rats, will help elucidate if this modulation is a component of sensorimotor coordination and if it is sufficient to exert influence on active sensing.

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active sensing, sensorimotor coordination, electrical microstimulation

Effect of Repeated Exposure to Sevoflurane on Physiologic and Electroencephalographic Features in Pediatric Patients Undergoing Radiation Therapy

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Background: Repeated exposure to drugs, such as opioids or benzodiazepines, leads to pharmacological tolerance. However, it has not been established whether the repeated exposure to sevoflurane, an inhalational anesthetic used especially in children, induces pharmacological tolerance.Methods: Here, we conducted an observational study in infants (n=11) requiring general anesthesia for radiotherapy treatment under a standardized protocol. Only sevoflurane was administered for Induction (8%) and Maintenance (2.5%) throughout all radiotherapy sessions. We record the “Induction time”, defined as the time between the beginning of the anesthetic administration and the insertion of the laryngeal mask once the unconsciousness is established. Every third session we recorded electroencephalographic signals with 4 frontal electrodes. We performed power spectral analysis over cleaned electroencephalographic windows recorded during Maintenance. To compare spectral power through radiotherapy sessions we used a multitaper frequency-domain bootstrap method. Based on this statistical we performed a pot-hoc paired t-test.Results: Throughout sessions, we found no differences in the Induction time. Our preliminary results show an attenuation in delta and alpha-band activity through sessions. Further paired comparison showed a significant decrement in delta-band power between the first and the last recorded session. Overall, our results suggest that repetitive exposure to sevoflurane does not induce tolerance.

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Sevoflurane, EEG, Pediatric population

The involvement of the GABAergic hippocampal system during aging and its relationship with cognitive performance in Octodon degus

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We evaluated the burrowing behavioral task (BT), which has been used to study cognitive abilities in rodents during aging. We used Octodon degus (degus) that can live 8-10 years. Also, we studied the GABAergic system of the hippocampus. At degus, we compared the performance in BT with a novel object recognition test (NOR) and the free open field test (OF). We studied animals between 25 and 71 months of age. We separated them according to the results of BT in Good Burrowers (GB) (n=11) and Bad Burrowers (BB) (n=14). Using the NOR and OF tests, we didn't find significant differences.We evaluated the hippocampal network using a matrix of 252 multi-electrodes. We calculated the firing rate (FR) under spontaneous activity (SA) and then added picrotoxin (PTX), a GABAa receptor antagonist. GB degus showed higher hippocampus inhibition than BB degus, reaching values with FR PTX (GB 2.0Hz+0.2; BB 1.5Hz+0.1). The maximum action and the percentage of neurons affected by PTX doubled in GB against 1.6-fold in BB and 52.9% in GB against 34.4% in BB, respectively. Then, we found that CA3, a region associated with memory processes and the hippocampal network core, presented a higher inhibition in GB degus, with a 6-fold increase compared to its SA (PTX=2.2Hz+0.5Hz; SA=0.35Hz+0.1Hz). Finally, we found in GB more interneuron (7.8%) than in BB (5%).Our results suggest that BT is an excellent test to separate our population of aged degus. GB degus maintained a better condition of the GABAergic system compared to BB degus.

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Aging Burrowing GABA

Allocentric episodic memory onset along postnatal development during sleep (Consolidación de la memoria episódica alocéntrica a lo largo del desarrollo postnatal en condición de sueño)

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

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electrophysiology, development, behaviour

Alternative Presurgical Language Paradigms for Inducing Crossed Cerebro-Cerebellar Language Activations in Brain Tumor Patients Using Functional Magnetic Resonance Imaging

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Crossed cerebro-cerebellar language lateralization activations observed with fMRI have recently come to light as an additional diagnostic feature for patients with brain tumors. The covert verb generation task is a widely used language paradigm to determine these language-related activations. Here, we propose two additional button-press language paradigms for this purpose, the semantic and phonological association tasks, as they are easy to monitor and easier to perform for patients whose language processing is affected by the presence of their tumor. Healthy subjects (n = 23) and patients with brain tumors localized at different cortical sites (n = 71) performed three language paradigms, namely the covert verb generation task as well as the semantic and phonological association tasks with button-press responses. Respective language activations in disparate cortical regions, as well as the cerebellum, were assigned laterality by a neuroradiologist blinded to task and handedness. All three tasks evoked significantly similarly lateralized language activation patterns in the cortical regions as well as the cerebellum in both participant cohorts. Additionally, a McNemar test confirmed the presence of crossed activations in the cortex and the cerebellum in the entire subject population. Here, we demonstrated that the semantic and phonological association tasks resulted in crossed cerebro-cerebellar language lateralization activations as those observed due to the covert verb generation task. This may suggest the possibility of these tasks replacing or used conjointly with the traditional verb generation task, especially for subjects that may be unable to perform the latter.

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Language lateralization, fMRI, brain tumor Low-frequencies and beta-band activity participate in scene processing.

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Our brain can categorize visual scenes in just hundreds of milliseconds while involving several cortical areas. Electroencephalographic recordings show that the P2 component, observed over lateral parietal sites, modulates its amplitude with scene properties. Despite our knowledge of the cortical areas involved, and the process's timing, the modulation of electroencephalographic frequency bands remains unknown. In this work, we study spectral power modulations related to the onset of natural scenes (NS) on healthy humans (n=18). Besides NS, subjects were presented with images created to control low (Pink noise) and high-level (Inverted) scene features. Additionally, White noise images were created from the original NS but with a flat spectrum. The effect of this last manipulation was that the main content of the image was visible but with a noisy overlay. We compared each category's spectrograms, from the right lateral parietal electrode, with plain gray images. Clusters of significant differences were identified using nonparametric statistical testing. We observed an early increased low-band (below 10 Hz) activity and decreased beta-band power for all categories compared to gray images. Specifically, we found large significant clusters of beta decrement for images with content (NS, Inverted, and White noise), indicating a beta-band role in high-level processing content. Only Inverted and White noise images show significant clusters of low-band enhancement sustained over hundreds of milliseconds. This last result might suggest a role of low-band power on cognitive effort. We conclude from these results that low-frequencies and beta-band modulation participate in visual-scene processing.

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EEG, perception, beta-band

Frontal Theta Phase Connectivity during Planning (Conectividad de fase theta frontal durante la planificación)

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Cognitive planning, the ability to develop a sequenced plan to achieve a goal, plays a crucial role in human goal-directed behavior. It has been suggested that cognitive control might result from frequency-specific interactions of specialized and widely distributed cortical regions due to the enriched rhythmic structure nature of the brain. In a previous study, using a novel and ecological planning task, a strong increase of frontal midline theta (FMθ) was induced by planning, and the prefrontal cortex theta activity sources were correlated with behavioral performance. However, the connectivity dynamics between frontal and distal sites and their relationship with planning behavior remain elusive. Using Weighted Phase Lag Index, we found a robust increase in theta phase connectivity during planning. Moreover, stronger theta phase connectivity was associated with planning performance. These results support the idea of cognitive control implementation is performed via theta phase connectivity which may be coordinating information, such as visuospatial analysis and motor control preparation, through the prefrontal cortex and disparate brain regions.

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planning, cognitive control, theta phase connectivity

Cortical responses to speech contrasts in preschoolers with Developmental Language Disorder

Respuestas corticales a contrastes de habla en preescolares con Trastorno del Desarrollo del Lenguaje

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Developmental Language Disorder (DLD) involves significant and persistent difficulties in native language acquisition. DLD aetiology is unknown, but theories suggest functional differences in speech cortical processing (see Evans & Brown, 2016 for a review). For adults with typical language development (TLD), speech cortical responses are enhanced by higher-level linguistic representations and greater language knowledge (Gansonre et al., 2018). However, it is unclear whether such influences are present during language development and if they vary with language proficiency. This study aimed to investigate differences in cortical Mismatch Responses (MMRs) to speech contrasts in 27 Chilean preschoolers (aged 4.9-5.7 years), 16 with a pre-existing DLD diagnosis and 11 TLD controls. Electroencephalography was recorded in a Multi-feature paradigm (Näätänen et al., 2004) during passive listening of the non-word /FUS/ (standard, 50% probability) and four deviants (12% each) produced by changing the standard initial phoneme. Thus, we manipulated the stimulus phonological (native vs non-native phonemes), lexical (word vs non-word) and semantic (content vs function word) content. Contrary to predictions, mean amplitude (Fz) did not differ significantly between groups for any deviant type. However, Mass Univariate Analysis (all electrodes) indicated an incidence of significant MMRs for all deviants in the DLD group, but only for non-words in the TLD group. Importantly, MMR effects were more positive, prolonged, and widely distributed for the DLD than for the TLD group, suggesting that group differences in speech MMRs may not rely upon conventional amplitude analyses but may lie in the topography, time-course and polarity of cortical activation patterns.

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Speech perception, Mismatch responses, Developmental Language Disorder

Remifentanil enhances propofol hypnotic clinical and electroencephalographic effect in humans during loss of consciousness

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Introduction: General anesthesia is a reversible pharmacological state in which patients are unconscious making surgery possible. As part of balanced general anesthesia, it is common to use the synergy between the hypnotic (propofol) and the opioid (remifentanil) to achieve the desired clinical effect. However, the electroencephalographic correlate of this synergy has not been fully studied.Methods: Here, we registered patients during anesthesia induction with a 4-frontal electrodes EEG monitor using two protocols. 1) PROPO (n=10): propofol infusion until Loss of Consciousness (LOC). 2) REMI-PROPO (n=10): remifentanil and propofol infusion until LOC. The EEG spectrum was obtained for both protocols during all induction until after LOC. We compared the spectra from both groups using bootstrapping analysis.Results:PROPO patients required higher propofol dose to achieve LOC compared to REMI-PROPO.REMI-PROPO patients have lower spectral alpha power before LOC, and higher delta power after LOC than patients in PROPO protocol.When PROPO had the same propofol concentration of REMI-PROPO after LOC onset, PROPO had lower alpha power compared to REMI-PROPO.Discussion:Remifentanil enhances propofol hypnotic clinical effect, which is correlated with electroencephalographic activity.Electroencephalographic synergy persists once the LOC is reached, evidenced by a higher delta power in those patients who only reach LOC with propofol, which is consistent with the higher concentration of propofol required to reach LOC.Lower alpha power in PROPO at the same dose of propofol in REMI-PROPO is consistent with the fact that PROPO patients have not reached the LOC at this dose.

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anesthesia, electroencephalographic, power spectra

Characterization of the psychobiological effects of environmental enrichment in children and adolescents with ntelectual disability: A systematic review (Caracterización de los efectos psicobiológicos del enriquecimiento ambiental en niños y adolescentes con discapacidad intelectual: Una revisión sistemática)

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Introducción: El enriquecimiento ambiental (EA) se define como una combinación contextual de estímulos inanimados y sociales complejos que facilitan habilidades sensoriales, motoras, cognitivas y socioemocionales. Este paradigma neurocientífico potencia la neuroplasticidad experiencia-dependiente, validándolo como un modelo de intervención aplicable al área educativa, neurológica, y de salud mental. Esto resulta prometedor en usuarios con discapacidad intelectual (DI), los cuales pueden ver afectado su desempeño funcional en estas tres áreas. El objetivo de esta investigación es caracterizar los efectos psicobiológicos del EA en niños y adolescentes con DI. Esto permitirá optimizar el diseño de políticas públicas e intervenciones de carácter educativo, social y de salud asociadas a este perfil de usuarios.Método: Se realizó una revisión sistemática según las directrices de la declaración PRISMA. Se emplearon 5 fases: identificación, selección, elegibilidad, inclusión y evaluación de sesgo. La búsqueda se realizó en las bases de datos Web of Science, Scopus, EBSCOhost y PubMed usando las palabras claves en inglés “environmental enrichment”, “intellectual disability”, “children” y “teens”, junto a sus sinónimos y extensiones desde el año 2000 a 2020.Resultados: La muestra fue de 10 investigaciones empíricas cuantitativas sobre intervenciones basadas en EA en niños y adolescentes con DI. Protocolos estandarizados de EA como el Feuerstein’s Instrumental Enrichment y UCLA PEERS School-Based Program generan mejoras sustanciales en la participación social, rendimiento cognitivo, habilidades lingüísticas y funciones ejecutivas como atención ejecutiva y memoria de trabajo. Se sugiere promover la investigación traslacional de EA.

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Analysis of transcriptional changes associated with CRE elements in a murine model of Huntington's disease given a variation in the levels of H3H27ac.

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Huntington's disease (HD) is a neurodegenerative disorder caused by an abnormal expansion in the number of CAG trinucleotide repeats within the HTT gene. In HD models, the mutant huntingtin protein (mHtt) is capable sequestering different proteins as a nuclear aggregate such as CREB-binding protein (CBP), causing a altered acetylation of neuronal histones, cellular toxicity and causing deregulation of the cAMP response element binding protein (CREB). Given this, CREB could decrease its transcriptional activity and therefore decrease the activity of the CRE element. In this work, using the information of HD murine models identify the variation in the acetylation levels of H3K27 and transcriptional changes associated with CRE elements.Our findings suggest that the decrease observed in the levels of acetylation of H3K27 (H3K27ac) in the genes close to CRE elements could be due to lower levels of CBP available when it is sequestered by mHtt. This findings explain the decrease of the CREB-CRE function and the observed lower activation levels of CRE related genes. Subsequently, we explain these effects by performing differential network analysis on networks representing the regulation of CRE associated genes created considering the variation in H3K27ac levels produced by the decrease in CBP activity.The decrease in H3K27ac levels in genes close to CRE is due to the possible decrease in CBP levels. Affecting the CREB-CRE function, having a lower activation of genes. The gene regulatory network provides information for further analysis, in order to determine the key genes and the essential TFs in HD
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Huntington disease, CREB binding protein, H3K27ac

Emergence of Synergistic interactions in small networks of neuronal oscillators. (Emergencia de interacciones sinérgicas en redes pequeñas de osciladores neuronales.)

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Synergistic interactions occur when the dependence of an element to the rest of the system is larger ná the sum of pairwise interactions with the other elements. Synergistic interactions have been measured in fMRI recordings of brain activity and shown to decline with aging. Synergy is a landmark of complex systems, however nális is known about how this type of interactions emerge in continuous dynamics such as neuronal networks. Using a basic model of neuronal oscillators, we aim to understand the relationship between topological and dimensional features of a dynamical system and the emergence of synergistic interactions. We simulated two or three connected Wilson-Cowan oscillators, sweeping the connectivity parameters and characterized the nature of the nálisis (limit cycles, q-Tori, chaotic or non-chaotic) by its estimated topological nálisis . At the same time, we measured the synergistic or redundant nature of the high-order interactions using the O-information measure. We found that both chaotic and toroidal attractors give rise to synergistic interactions between the system variables, while limit cycles of nálisis lower ná two are characterized by redundancy of the time series, for the two and three-nodes network. nálisi three-nodes network, we searched for the connectivity parameters that maximize synergy, consistenlty finding a motif of one independent node that influences the other two. Our work is a first step towards understanding how synergy emerges from simple dynamical systems, and nál help to understand what the measurement of synergy in brain activity can tell us about its structure in health and disease.

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Synergy, Neuronal Networkds, Dynamical Complexity

Verbal fluency and thematic coherence markers nálisis in ultra-high risk for psychosis (UHR).
(Análisis de marcadores de fluidez verbal y coherencia temática en personas con estados mentales de alto riesgo de psicosis (EMARS))

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Proponemos un análisis de marcadores lingüísticos (ML) presentados frecuentemente en esquizofrenia (EQZ) en población con sospecha de primer episodio de psicosis. Los ML estudiados se relacionan con mejor rendimiento informativo, demostrados en trabajos previos sobre el lenguaje de personas con EQZ: los marcadores de fluidez verbal y gestión del tema. Estos pacientes presentan alteraciones tempranas en la funcionalidad lingüística. Recientemente se ha observado la utilidad de estos ML como predictores de psicosis utilizando técnicas de lenguaje automatizado alcanzando precisión igual o superior a herramientas clínicas tradicionales.Objetivo: Identificar la presencia de ML propios de la EQZ en personas con sospecha de psicosis.Se analizaron factorialmente ML de 18 entrevistas clínicas en pacientes con sospecha de EQZ y diagnóstico de primer episodio de EQZ, determinando variables asociadas significativa y positivamente con variables demográfico-clínicas. La correlación más informativa se da entre aspectos disfuncionales de la coherencia temática y fluidez verbal, explicando hasta un 78% de la varianza.Por tanto, se observa un deterioro temprano de la fluidez verbal en personas con sospecha de EQZ; por pausas extensas y volumen léxico disminuido. La coherencia temática en el grupo con sospecha diagnóstica presenta incipientes disfunciones, siendo en el primer episodio donde se manifiestan de forma significativa ambos tipos de ML.
Financiado por FONDECYT 11191122Psicosis, Primer episodio, Marcadores lingüísticos

Functional consequences of the comorbidity between Anxiety Disorders (AD) and Attention Deficit Hyperactivity Disorder (ADHD) in Chilean children and adolescents (NNA).
(Consecuencias funcionales de la comorbilidad entre Trastornos de Ansiedad (TA) y Trastorno por Déficit Atencional e Hiperactividad (TDAH) en NNA (niños, niñas y adolescentes) chilenos.)

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Introduction: 22.4% of Chilean children and adolescents have a psychiatric disorder that causes them disability. The primary disorders that affect them are disruptive (14.6%, of which ADHD alone represents 10.3%) and AD (8.3%) and the association between both disorders is very frequent, both in the general population and in clinical samples (ranging from 25-50%).Research Question: What are the functional consequences of the comorbidity between ADHD and AD?Hypothesis: The comorbidity between AD and ADHD in NNA reduces children and adolescent's emotional functionality, deteriorating their overall functionality.Materials and Methods: Clinical study with NNA, carriers of this comorbidity and controls who underwent a clinical evaluation (interview by a specialist and application of scales) and assessment of their behavioral response (through an emotion recognition task).Results: Comorbidity anticipates the age of consultation, affects both sexes similarly, and intensifies both anxiety and attentional symptoms. In addition to the anxiety symptoms associated with isolated ATs, social phobic traits were more frequent in NNA who had this comorbidity. In terms of attentional symptoms, elements of hyperactivity / impulsivity were added to inattention. The foregoing, impacts school, cognitive and social functionalities, and compromises emotional functionality as observed in the emotional discrimination task, in which they presented worse performance and prolonged reaction times both during the identification of emotions and distractors.Conclusion: The existence of this comorbidity significantly deteriorates the overall functionality of children and adolescents, in a more significant proportion than only an additive effect between both conditions, leading to a synergistic interaction between both.

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ADHD, ANXIETY DISORDERS, COMORBIDITY

Fine scale organization and function of cholinergic inputs onto midbrain dopaminergic neurons

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Midbrain dopaminergic neurons are involved in various functions including motor control, motivation and behavioral reinforcement. Their dysfunction is related to disorders such as Parkinson's disease, depression, schizophrenia and addiction. Cholinergic and glutamatergic neuronal afferent systems excite and promote burst firing in dopaminergic (DA) neurons. Acetylcholine released from cholinergic terminals influences DA neurons through direct postsynaptic action, but also via facilitation of presynaptic glutamate release. This latter action is mediated by presynaptic nicotine receptors and, in the context of tobacco consumption, has been shown to be critical in the addictive properties of nicotine. In order to reveal the structural basis of this interaction, we analyzed the physical arrangement of the presynaptic cholinergic and glutamatergic terminals and postsynaptic dopaminergic elements. We worked with the underlying hypothesis that presynaptic terminals locate close to each other such as to optimize the influence of volume-transmitted acetylcholine onto DA neurons. For this purpose, mouse brain tissue was treated for triple immunohistochemistry for cholinergic, glutamatergic and dopaminergic markers and observed with confocal microscopy. Dendrites of DA neurons and the afferent terminals where reconstructed and analyzed stereologicaly. Preliminary results of this study show that there is no spatial aggregation of glutamatergic and cholinergic terminals on DA dendrites. However, there appears a positive relationship between the size of cholinergic terminals and the diameter of the DA dendrite, something not observed for glutamatergic terminals, suggesting a differential influence of these afferent systems onto postsynaptic structures. Further structural analysis will allow a better characterization of this important tripartite synaptic arrangement.

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Dopamine neurons, Acetylcholine, Glutamate

Extending the integrate-and-fire model to account for metabolic dependencies

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It is widely accepted that the brain, like any other physical system, is subjected to physical constraints restricting its operation. The brain's metabolic demands are particularly critical for proper neuronal function, but the impact of these constraints is still poorly understood. Detailed single-neuron models are recently integrating metabolic constraints, but the computational resources these models need, make it difficult to explore the dynamics of extended neural networks imposed by such constraints. Thus, there is a need for a simple-enough neuron model that incorporates metabolic activity and allows us to explore neural network dynamics. This work introduces an energy-dependent leaky integrate-and-fire (LIF) neuronal model extension to account for the effects of metabolic constraints on the single-neuron behavior (EDLIF). This simple energy-dependent model shows better performance predicting real spikes trains -in spike coincidence measure sense- than the classical leaky integrate-and-fire model. It can describe the relationship between the average firing rate and the ATP cost, and replicate a neuron's behavior under a clinical setting such as amyotrophic lateral sclerosis. The simplicity of the energy-dependent model presented here, makes it computationally efficient and thus, suitable to study the dynamics of large neural networks.

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homeostasis, energy, single-neuron model

Contribution of spontaneous blink rate in perceptual stability

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Bistable stimuli are commonly used to understand the mechanisms of visual perception, under the assumption that the stimulus that reaches the retina is invariant—however, spontaneous acts like blinking block sensory input for 250 milliseconds, interfering with visual processing. ¿Can blinking contributes to a greater or lesser perceptual change? We hypothesized that the decrease in the spontaneous blink frequency is associated with greater perceptual stability. We studied this behavior in subjects subjected to a visual task by presenting three bistable stimuli (Necker's cube, Plaids, and Structure from motion). They carried out two conditions; a free visual exploration of the images and reporting when they perceived a perceptual change. The second condition is to fix our gaze on a central point under the same paradigm. We observed that during a free scan, an increase in the blink rate occurred from -1500 to -800 ms before the report of perceptual change. Then a decrease in blinking is observed. This decrease in blink frequency occurs from -500 milliseconds to 500 milliseconds after the report in the gaze condition. When analyzing the figures separately in the SFM and Plaids free exploration, a decrease in flicker is observed from -800 milliseconds until the report. For the Necker cube, the decrease is observed from -500 milliseconds. Our results support the idea that decreasing the frequency could contribute to perceptual stability.

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Blinks, Visual perception, Bistable stimuli

Disynaptic, VTA-mediated, cerebellar modulation of the prefrontal cortex (El cerebelo modula la corteza prefrontal via relevo sináptico en el area tegmental ventral (VTA))

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The cerebellum (Cb) has been associated with cognitive disorders that potentially affect the medial prefrontal cortex (mPFC), such as schizophrenia and autism. However, how the cerebellum affects the mPFC remains to be established. The mPFC is thought to be involved in decision-making processes that guide behavior based on predicted outcomes. The ventral tegmental area (VTA) is a key region of the brain reward system that provides reward-related signals to the mPFC via dopaminergic projections. We have recently shown that the Cb sends direct excitatory projections to the VTA, raising the possibility that there might be a disynaptic pathway from the Cb to the mPFC via the VTA. Here we describe experiments aimed at delineate the anatomical and functional properties of the Cb->VTA->mPFC circuit in the mouse brain. Using intersectional tracing, we found that ~50% of VTA neurons that receive inputs from the Cb also send direct synaptic projections to the mPFC, confirming the presence of this disynaptic circuit. Using in vivo recordings in head-fixed awake mice, we found that optogenetic stimulation of Cb axons in the VTA excites mPFC cells within a fast time scale (average latency of 31.9 ± 13 ms). Moreover, by using fiber photometry we show that optogenetic activation of Cb axons in the VTA releases dopamine in the mPFC, supporting the functional connectivity of the proposed circuit. These results show that the cerebellum might have a direct contribution to cortical dopamine levels, pointing to dopamine deregulation as a possible link between cerebellar dysfunction and mental disorders.
NIDA 1R01DA044761-01A1
Reward, Dopamine, Goal directed behavior

POSTER SESSION II

Effects of a ketogenic diet at short, medium and long-term on cortical synaptic proteome in aging mice

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Aging is a complex process characterized by a sustained decline of physiological performance of organs over time, with increased risk of suffering chronical diseases and mortality. The prefrontal cortex is a brain structure particularly vulnerable with age, evidenced by dramatical anatomical and metabolic changes, which leads to compromised neuronal activity and loss of cognitive abilities. In vitro studies in cortical neurons, suggests that loss of synaptic proteins homeostasis is one of the main age-related molecular events responsible of working memory and learning impairments. Nevertheless, despite big efforts focused on identification of biomarkers implicated on these complex disorders, there is still lacking effective treatments to tackle the proteostasis imbalance and their detrimental effects. Recently, ketogenic diet (KD), a low-carbohydrate high-fat diet, has emerged as a powerful nutritional intervention, able to induce a metabolic switch and memory preservation in aged male mice fed by 12 months. However, a detailed analysis of KD administration-term and specific modulation on the synaptic proteome contributing to the cognitive improvements previously reported, remains to be elucidated. This work addresses such questions, assessing the effects of KD in the synaptic proteome of old male mice, through a short, medium and long-term administration by mass spectrometry analysis of synaptosomes, a biochemically isolated fractions enriched in synaptic connections. Altogether, the current research provides new insights in the age-related synaptic proteome alterations and it shed lights on possible molecular targets modulated by a metabolic switch induced by KD, which potentially contributes to preserved synaptic network at advanced age.

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Aging, Ketogenic diet, Synaptosome

Characterization of the senescent-like phenotype in culture-aged neurons and its impact on the establishment of synaptic contacts

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Cellular senescence was characterized in proliferation-competent cells and thus defined as a permanent cell cycle arrest. From this perspective, neurons, given their post-mitotic nature, are unable to senesce. However, as neurons age, some become apoptosis resistant and express several senescence markers. This phenotype is therefore called the “senescence-like phenotype”. One of the milestones of senescence is DNA damage, particularly double strand breaks (DSBs), which neurons accumulate because of their metabolic profile. Neurons, unlike other cell types, depend mainly on oxidative phosphorylation rather than glycolysis to survive, therefore undergoing larger amounts of oxidative stress.Neurons displaying the senescence-like phenotype exist within the context of the aging brain, where the number of neurons remains mostly unaltered throughout the life cycle of an organism, yet some regions of the brain show an important decline in the number of synaptic contacts. Isolating “senescent-like” neurons in vivo is a complicated task, nevertheless in long-term cultures, some neurons acquire this phenotype. We seek to characterize the senescence-like phenotype in long-term hippocampal neurons using canonical senescence markers such as senescence-associated β-galactosidase, γ-H2AX phosphorylated histone, the expression of IL6 an IL1a, and to asses the number of synaptic contacts via the colocalization of pre and postsynaptic markers.After 30 DIV, we have characterized neurons which are positive for the phospho-histone γH2AX and an increase in the expression of the SASP component IL6. However, no changes in SA-β-galactosidase staining were observed between different stages. Quantification and analysis of synaptic contacts did not deem significant differences within stages either.

Fondecyt 1180419, FONDAP 15150012
Neuronal senescence

Direct reprogramming of fibroblasts into chemically induced neurons following a small-molecule based protocol (Reprogramación directa de fibroblastos hacia neuronas quimicamente inducidas utilizando una estrategia farmacológica)

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The study of brain aging at is limited because murine neuronal models are mainly restricted to embryonic stages and the technical and ethical impossibilities to study human neurons. Nevertheless, direct reprogramming of somatic non-neuronal cells into functional neurons maintains age-associated features from the donor, which allows us to study aging in a cellular level. We implemented a cell-reprogramming methodology based in a pharmacological treatment. We reprogrammed mouse embryonic fibroblasts (MEF) and adult mouse dermal fibroblasts from young and old animals into chemically induced neurons (ciN). After the pharmacological treatment cells exhibit dramatic morphological changes, acquiring neuron-like morphology. After 7 days post-induction (dpi) cells start expressing the canonical neuronal marker βIII-tubulin as detected by immunocytochemistry and real-time quantitative PCR. As induction progresses cells increase expression levels of βIII-tubulin reaching its maximum of expression at 21 dpi. Classical neuronal cytoskeletal elements such as the somato-dendritic microtubule-associated protein 2 (MAP2), the axonal protein tau and poly-glutamylated tubulin were also detected in ciNs. Glutamatergic synaptic proteins such as synaptophysin-I and Homer 1 were also expressed at 21 dpi ciN. Finally, single-cell electrophysiological recordings show that the ciN present outward potassium currents elicited by different voltage pulses. To promote further maturation of ciN, we have co-cultured them with primary postnatal astrocytes and observed greater processes extension and branching, which indicates greater maturation stages. Further efforts will be focus on reaching maturation stages where ciN show different cell features of mature neurons, to obtain fully functional ciN from young and old donors.

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Characterization of Cdk5/p35 expression and function in tissue section and primary culture of nodose neurons from rodents.

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The Nodose Ganglia (NG) contain sensory neurons of the vagus nerve, which innervate viscera and convey sensory information to the CNS. Nodose neurons express several receptor-channels implicated in sensory modalities, such as mechanoception, chemoception and nociception. However, important proteins and molecular mechanisms implicated in these processes are not fully understood. Previously, we reported Cdk5/p35 complex, an important kinase implicated in numerous cellular processes in central and peripheral neurons, is present in NG. Here, we evaluate morphology, receptor-channels expression and Cdk5 activity in NG sections and in primary cultures of NG neurons. We detected three major cell types in NG section cuts: satellite glial cells (GS), nodose neurons (βIII-tubulin+) and Schwann cells (MBP). Using immunostaining and confocal microscopy, we found a high co-distribution of Cdk5 with p35 in NG neurons. Cdk5 also co-localized with two relevant phosphorylation substrates implicated in pain signaling, TRPV1 and P2X2R, in NG neurons. Most importantly, we detected Cdk5-mediated TRPV1 phosphorylation in NG neurons suggesting that Cdk5 is active in this tissue. Moreover, we obtained preliminary results of Cdk5 expression in NG from conditional knockout mice for Cdk5 (Cdk5 cKO) in Nav1.8+ neurons. We found that Nav1.8 is highly expressed in NG neurons, co-localizing with Cdk5, p35, TRPV1 and P2X2R. Additionally, we found decreased Cdk5 expression in NG neurons from Cdk5 cKO mice. In conclusion, our results showed that Cdk5 is active in NG, suggesting a potential involvement in NG neuron functions.

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Cdk5, Nodose neurons, TRPV1 phosphorylation

Estradiol activates the heat receptor TRPV1 channel

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The TRPV1 channel, also known as the heat and capsaicin receptor, responds to a variety of physicochemical stimuli, including noxious heat, the active compound of chili peppers capsaicin, and is also involved in physiological and pathological pain perception. This is a nonspecific six-spanning membrane segment cationic tetrameric channel, expressed in a subpopulation of cells in the dorsal root and trigeminal ganglia, that innervates the body and the face. It is also found in other neuronal and non-neuronal cells types such as hippocampal neurons and visceral tissues. Estradiol is a key hormone in male and female development and is involved in a variety of physiological and pathophysiological processes. Previous work has been demonstrating that 17β-Estradiol (E2) can protect hippocampal neurons from oxidative stress modulating TRPV1 activity, independently of estrogen receptors expression. Here we show that E2 enhances TRPV1 channel activation when expressed in Xenopus laevis membranes as measured by macroscopics and single channel recordings. E2 administration induces a large leftward shift in G/V relationships of -85 mV at 1 µM concentration. By molecular modeling followed by molecular dynamics analysis using the open structure of TRPV1 (PDB: 3J5R) we found that E2 binds to the vanilloid pocket, where hydrophobic and polar interactions can be identified with the following residues, LEU515, ASN551, SER512, ALA566 and ARG557, and this last one also interacts with capsaicin. Our findings reveal that E2 is an important modulator of TRPV1 activity.

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Early functional NMDA Receptors contribute to hippocampal axonal outgrowth through Rac1 activity, actin cytoskeleton dynamics and hydrogen peroxide production.

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NMDA Receptors (NMDARs) play essential roles in the development and functionality of the nervous system which are activated by neurotransmitter glutamate to mediate Ca2+ influx. However, the contribution of NMDARs to the early neuronal development it is still unexplored. Although NMDARs classically act at postsynaptic membrane, here we found that NMDARs are expressed and functional during neuronal polarity acquisition and importantly endogenous and transfected NMDARs are distributed in the axonal compartment early in development. Moreover, NMDARs loss- and gain-of-function altered neuronal polarization and axonal elongation by a mechanism that involves both Rac1 activity and actin cytoskeleton dynamics. In addition, we found that NMDARs activity regulates hydrogen peroxide (H2O2) production, essential signaling molecules that support neuronal development. Thus, NMDARs signaling promotes a Rac1 dual function to mediates both actin cytoskeletal remodeling and H2O2 production by the NADPH oxidase complex. Altogether, these findings suggest that early physiological glutamate presence activates NMDARs to support neuronal development previous to synapse formation, supporting the notion that glutamate is not only necessary for neurotransmission but also for early neuronal development and axonal growth.

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NMDA receptors, Axonal growth

Panexina-1 regula la ramificación dendrítica y la formación de espinas dendríticas en neuronas del hipocampo a través de la modulación del citoesqueleto de actina vía actividad Rho GTPase Rac1.

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Small Rho GTPases, RhoA, Rac1, and Cdc42 plays an essential role in neuronal morphology regulating dendritic arborization, spine morphogenesis, and axon guidance and growth, by controlling the assembly and stability of the actin cytoskeleton. Changes in Rho GTPases signaling are associated with several neurodevelopmental and neurodegenerative diseases, including autism, intellectual disability, and Alzheimer's disease. However, it is relatively unknown the signals that control their activation or inhibition under neuronal development and plasticity. Pannexin-1 (Panx1) is a membrane protein that forms non-selective channels which have been implicated in actin-dependent processes such as cell migration and neurite extension, but their involvement in other structural changes such as those associated with synaptic plasticity is missing.We investigate if Panx1 channels modulate actin remodeling-dependent structural plasticity in the mouse hippocampus. In the absence or blockade of Panx1, pyramidal neurons of the CA1 region exhibited a higher dendritic complexity and dendritic spines density after the induction of chemical long-term potentiation by glycine stimulation compared to control neurons. In addition, the absence or blockade of Panx1 channels stimulated the polymerization of F-actin and increased the expression of actin-related proteins. Interestingly, pull-down assays of hippocampal homogenates revealed that the absence of Panx1 channels increased Rac1 activity, whereas inactivated RhoA under basal conditions. Nevertheless, glycine stimulation of hippocampal slices induced activation of RhoA, Cdc42, and Rac1 in all groups. Our results provide evidence that the role of Panx1 channels in neuronal morphology and structural synaptic plasticity relies on actin organization and dynamics, by regulation of Rac1 GTPase activity.

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structural plasticity, actin-cytoskeleton, Pannexin-1

Cornifelin expression in the frog Xenopus laevis during metamorphosis (Expresión de Cornifelina en la rana Xenopus laevis durante la metamorphosis)

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The frog Xenopus laevis presents a unique model due to the characteristics of their lifecycle, making it possible to make comparisons between pre- (regenerative, R) and post-metamorphosis stages (non-regenerative, NR). A high throughput mRNA sequencing was done in our laboratory to identify genes expressed in R and NR-stages animals after spinal cord injury. This study found that cornifelin was one of the transcripts with the highest expression in NR-animals after two days of injury. In contrast, in R-animals the levels were unaltered (Lee-Liu D, 2014). Cornifelin is a 111 amino acid protein expressed in corneocytes from damaged skin (Michibata H, 2004). Besides, it is related to differentiation and cell- adhesion both in the skin and oral mucosa (Wagner T, 2019).Until the report by Lee-Liu, the expression of cornifelin in the spinal cord was unknown. So far, the localization in the central nervous system has not been studied. In this work, we used RT-qPCR and immunohistochemistry techniques, and here we show that cornifelin is not only expressed in the spinal cord but also in the eye. We found cornifelin in meninges and the grey matter of the spinal cord. In the latter, the expression decreased during metamorphosis, being the lowest at NR stages. On the other hand, in the retina, we found cornifelin in the photoreceptor layer, the inner and outer nuclear layers, and the ganglion cell layer. These results show that cornifelin is not only a skin protein but also might have a role in the central nervous system.

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spinal cord, development

Mesenchymal Stem Cell Secretome (MSC-S) administration reduces oxidative stress and neuroinflammation, improving cognitive functions impaired by Perinatal Asphyxia. (La administración de Secretome derivados de células madre mesenquimales (MSC-S) reduce el estrés oxidativo y la neuroinflamación, mejorando las funciones cognitivas deterioradas por la asfixia perinatal.)

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rinatal Asphyxia (PA) is a leading cause of motor and neuropsychiatric disability associated with sustained neuroinflammation, oxidative stress, and cell death affecting the surviving neonate. With a rat model of global PA, this study investigated the neuroprotective effects induced by intranasally administered MSC-S. PA was induced by immersing fetus-containing uterine horns into a water bath at 37 °C for 21 min. Two hours after birth and at postnatal day (P)7 MSC-S (6 µg protein in 16 µl derived from $2x10^5$ preconditioned-MSCs) or vehicle were administered intranasally to asphyxia-exposed or control rats. Oxidative stress was monitored in hippocampus by the GSSG/GSH ratio (at P7 and P60), NRF-2 nuclear translocation, and HO-1 and NQO1 levels by Western blots (WB) and RT-qPCR. Neuroinflammation was evaluated by NFκB/p65 nuclear translocation (WB) and IL-1β and TNF-α proinflammatory cytokines (RT-qPCR). Cell death was analyzed by cleaved caspase-3 protein level (WB). Anxiety (P30) was evaluated by open field and recognition memory by the novel object paradigm (P30). MSC-S administration: (i) lowered the PA-increased GSSG/GSH ratio; (ii) increased antioxidative NRF-2 translocation and NQO1 protein levels (iii) decreased nuclear NFκB/p65 translocation, and proinflammatory cytokines expression, and (iv) reduced cleaved caspase levels. These beneficial effects were accompanied by amelioration of anxiety and memory deficits. Overall, the study demonstrates that intranasal administration of preconditioned MSC-S is a novel therapeutic strategy that prevents the long-term effects of perinatal asphyxia.

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mesenchymal stem cell secretome, neonatal hypoxia, neuroprotection

Neuroprotector effect of IGF2 in aSyn-induced neuronal death, promoting aSyn secretion in Parkinson's disease models. (Efecto neuroprotector de IGF2 en la muerte neuronal inducida por aSyn, promoviendo su secreción de modelos de la enfermedad de Parkinson.)

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Introduction. Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra and the consequent appearance of motor symptoms. The presence of intracellular aSyn aggregates is considered its primary neuropathological factor, leading to neurodegeneration that culminates in neuronal death. Studies show that secretion of aSyn promotes dopaminergic neuronal survival. Neurotrophic factors have been therapeutic potential benefits for ND. In this context, Insulin-like growth factor 2 (IGF2) have been described has neuroprotective effect in ND decreasing protein aggregates in mice models. However, the effect of IFG2 in PD have not been elucidated. Materials and methods: SHSY5Y cell line and cortical neurons at 6DIV were incubated with aSyn PFFs and monomers. As a treatment, neuronal cultures were treated with recombinant IGF2 and overexpression using adeno-associated virus to transduce cortical neurons. After 3 days, viability assay was performed by Propidium Iodide stain. aSyn aggregates was evaluated after 6 days of incubation by western blot analysis. Additionally, cleaved caspase 3 was determined by immunofluorescence. Results: Our results show that IGF2 treatment decreases cell death in cortical neurons, accompanied with a decrease of caspase 3 activation. Additionally, IGF2 dramatically promoted a decrease in aSyn intracellular protein levels, increasing aSyn secretion in SH5YSY cells. Additionally, we observed that IGF2 treatments promotes a reduction of aSyn aggregates levels in primary cortical neurons. Discussion: These results suggest that IGF2 has a neuroprotective effect in aSyn-induced neuronal death, decreasing aSyn intracellular levels promoting aSyn secretion as a neuroprotective mechanism.

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IGF2, aSynuclein, neuroprotection

Evaluation of neosaxitoxin as an antiepileptic drug in an animal model of temporal lobe epilepsy.
(Evaluación de neosaxitoxina como fármaco antiepiléptico en un modelo animal de epilepsia del lóbulo temporal)

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This work aimed to evaluate the potential antiepileptic effect of neosaxitoxin (NeoSTX), a phycotoxin that selectively blocks voltage-gated sodium channels, with long-lasting, reversible, and non-neurotoxic effects, in an animal model of temporal lobe epilepsy (TLE).Immediately after inducing status epilepticus by intrahippocampal injection of kainic acid, the animals were randomly divided into four experimental sets (n=4 each): rats injected, during epileptogenesis and in the chronic stage, with NeoSTX (10 ng/ul) or saline as control. The local field potential (LFP) was recorded, while the behavior of all animals was video-monitored during the chronic stage 2 hours daily for a week. The degree of reactive gliosis was quantified by immunohistochemistry and the hippocampal functionality was evaluated by an object recognition memory task, before and after the experimental intervention.The suppression of the hippocampal electrical activity during epileptogenesis did not affect the development of the chronic stage, being comparable with the control group. Nevertheless, when NeoSTX was administered during the chronic stage, the incidence of LFP high-frequency events and the number of seizures decreased significantly after each injection compared to saline-treated animals. This observation paralleled with an improvement in the memory capacity of rats, yet the effect of NeoSTX on astrogliosis was not significant in the period observed.NeoSTX has potential as an antiepileptic drug since effectively reduces the number of seizures in this model of TLE. Further analysis is required to determine if this pharmacological intervention has neuroprotective effects, especially if the treatment period is extended or a different dose of NeoSTX is administered.Instituto Milenio, ICM P09-015F (Biomedical Neuroscience Institute, BNI, 2018-2022)
Neosaxitoxin, Temporal lobe epilepsy, Status epilepticus

Modulation of Panx1 opening by NMDAR in neurons of the spinal cord of neuropathic rats: evaluation by incorporation of YoPro1 (Modulación de apertura de Panx1 por NMDAR en neuronas de la medula espinal de ratas neuropáticas: evaluación por incorporación de YoPro1.)

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El dolor-crónico se caracteriza por amplificación de la información nociceptiva, (sensibilización central). El receptor NMDA(NMDAR) es el principal receptor/canal involucrado en la transmisión espinal del dolor-crónico. Nuestro laboratorio mostró que inhibición del canal Panexina1(Panx1) con péptido antagonista 10Panx reduce el dolor-crónico en ratas neuropáticas (RNp), implicando (primera vez) a Panx1 en la transmisión espinal nociceptiva. Ahora estudiamos la relación entre NMDAR y Panx1, evaluando la incorporación del colorante-YoPro1 en neuronas de rebanadas de médula espinal de RNp y su variación en presencia de antagonistas de NMDAR y Panx1. Adicionalmente estudiamos el rol de la tirosina-quinasa-Src en esta interacción.Día 7 post-cirugía ratas fueron anestesiadas, medula espinal extraída, región (L3-L5) cortada en vibratomo (200µm). Rebanadas fueron transferidas a cámara de incubación (37ºC-ACSF-burbujeo-O2/CO2) siendo pre-tratadas según protocolo 10panx(300µM), DAP5(50µM) o PP2(3,3mM) por 10 min y tratadas con NMDA+glicina(0,6mM+0,6uM) por 20 min, finalmente incubadas con YoPro1(5µM). Neuronas se identificaron por inmunofluorecencia y se cuantificó la incorporación de colorante por CONFOCAL.La estimulación de rebanadas con NMDA incremento la incorporación de YoPro1 en neuronas (Lamina Rexed I-II) de ratas sham, pero no neuropáticas. En RNp la administración de 10panx, DAP5 o PP2 disminuyó la incorporación de YoPro1, pero no sus respectivos controles.En RNp la sensibilización central mantiene la apertura de Panx1 al máximo. La estimulación del NMDAR induce apertura de Panx1 y al parecer esta apertura se encuentra mediada por la enzima Src-quinasa en neuronas espinales, sugiriendo que los efectos de activación del NMDAR son, en parte, mediados por la apertura de Panx1.

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dolor cronico, canal panexina 1, incorporacion colorante

A centronuclear myopathy-causing dynamin-2 mutation produces structural and functional impairments in the hippocampal excitatory synapses of a murine model of the disease

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Dynamin-2 is a ubiquitously expressed large GTP-ase, member of the Dynamin-Superfamily, that regulates membrane remodeling and cytoskeleton dynamics and orchestrates endocytosis, exocytosis, mitochondrial segmentation and intracellular trafficking. In the mammalian nervous system dynamin-2 modulates synaptic vesicle recycling at the nerve terminals and signaling receptor trafficking at the postsynaptic densities (PSDs). Mutations in dynamin-2 cause an autosomal dominant form of centronuclear myopathy (CNM), a congenital neuromuscular disorder characterized by progressive weakness and atrophy of distal skeletal muscles. Although CNM-mutations in dynamin-2 cause a muscle-specific disease, some reports describing learning disabilities and cognitive defects in CNM-patients suggest a concomitant synaptic impairment at the central nervous system. To evaluate this possibility we used heterozygous knock-in mice harboring the p.R465W mutation in dynamin-2, the most common causing CNM. These mice exhibited a reduced capability to learn and acquire spatial memory measured with Barnes-maze and novel-object-recognition tests. These cognitive defects correlated with impaired long-term depression and long-term potentiation of the excitatory synaptic strength. These synaptic plasticity defects were associated with reduced dendritic spines density and decreased glutamate AMPA-receptors availability at the PSDs. These results show for the first time that structural and functional synaptic defects occur in the CNM context and contribute to the still scarce knowledge about the importance of dynamin-2 at central synapses.

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c-Abl activation by Aβ fibrils promotes axon initial segment disassembly and tau missorting in hippocampal neurons (Activación de c-Abl por fibrillas Aβ promueve el desensamble del segmento inicial del axón y deslocalización de tau en neuronas hipocampales)

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Introduction: The axon initial segment (AIS) is a structural feature of neurons involved in the generation of the action potential. Recently, it has also been described as a submembrane diffusion barrier that prevents the diffusion of tau, an axonal microtubule associated protein, into the somatodendritic compartment. In Alzheimer's disease (AD), this barrier fails and hyperphosphorylated tau diffuses into the soma. C-Abl is a non-receptor tyrosine kinase that is activated by Aβ, mediating neurodegenerative and apoptotic cell responses. A functional link between the AIS and c-Abl hasn't been described to date.Materials and Methods: Hippocampal neurons were treated with fibrillary Aβ and c-Abl inhibitors Imatinib and GNF2, and (i) AnkG immunostaining, (ii) tau missorting into the somatodendritic compartment, and (iii) c-Abl activation were studied by immunofluorescence and western blot assays.Results: Short fibrillary Aβ insults (15 minutes to 4 hours) decrease the number of neurons that express AnkG in the AIS, increase tau missorting into the somatodendritic compartment, and generate an increase in the activation of c-Abl. The inhibition of c-Abl prevented AIS disassembly and tau missorting.Discussion: Aβ fibrils have a deleterious effect on AnkG integrity, allowing tau to migrate into the soma. Also, the activation of c-Abl participates in the disassembly of the AIS, as shown by the use of its pharmacological inhibitors. The AIS disassembly could represent one of several events in the amyloid cascade that culminate in the synaptic disfunction and cell death observed in AD.

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Alzheimer, C-Abl, Axon initial segment

Impaired intracellular trafficking of sodium-dependent vitamin C transporter 2 contributes to the redox imbalance in Huntington's disease (Alterado trafico del transportador de vitamina C dependiente de sodio 2 contribuye a imbalance redox en la enfermedad de Huntington)

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Huntington's disease (HD) is a neurodegenerative disorder caused by a glutamine expansion at the first exon of the huntingtin gene. Huntingtin protein (Htt) is ubiquitously expressed and it is localized in several organelles, including endosomes. HD is associated with a failure in energy metabolism and oxidative damage. Ascorbic acid is a powerful antioxidant highly concentrated in the brain where it acts as a messenger, modulating neuronal metabolism. It is transported into neurons via the sodium dependent vitamin C transporter 2 (SVCT2). During synaptic activity, ascorbic acid is released from glial reservoirs to the extracellular space, inducing an increase in SVCT2 localization at the plasma membrane. Here, we studied SVCT2 trafficking and localization in HD. SVCT2 is decreased at synaptic terminals in YAC128 male mice. Using cellular models for HD (STHdhQ7 and STHdhQ111 cells), we determined that SVCT2 trafficking through secretory and endosomal pathways is altered in resting conditions. We observed Golgi fragmentation and SVCT2/Htt-associated protein-1 mis-colocalization. Additionally, we observed altered ascorbic acid-induced calcium signaling that explains the reduced SVCT2 translocation to the plasma membrane in the presence of extracellular ascorbic acid (active conditions) described in our previous results. Therefore, SVCT2 trafficking to the plasma membrane is altered in resting and active conditions in HD, explaining the redox imbalance observed during early stages of the disease.

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ascorbic acid, neurodegeneration, neuron-glia interaction

Reactive Oxygen Species modulate Amphetamine induced effects

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The increase of dopamine (DA) in the reward system is related to the reinforcing effects of drugs of abuse and hyper locomotion induced by psychostimulants (Kuczenski et al.1991; Lüscher & Ungless, 2006; Lüscher & Malenka, 2011; Miller et al. 2014). Interestingly, it has been showed that ROS could modulate psychomotor response and reinforcing effects induced by drugs of abuse as cocaine and methamphetamine (METH) (Numa et al., 2008; Jang et al.,2016; Beiser et al., 2017). Nevertheless, the relation of ROS and AMPH has not been evaluated. To evaluate this relation, we studied the effect of the co-administration of AMPH and 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL), a ROS scavenger, on rats. To evaluate behavioral changes induced by administration of these drugs we analyzed the locomotor activity after AMPH (I.P; 1.5 mg/kg) or TEMPOL/AMPH (I.P; 100 mg/kg; 1.5 mg/kg) administration. Our results showed that TEMPOL attenuates AMPH enhancement of locomotor activity. After the behavioral test we performed immunofluorescence on brain slices obtained from these animals to evaluate changes in the oxidative cellular balance induced by administration of these drugs. Our results showed that TEMPOL also attenuates the oxidative stress induced by AMPH in nucleus accumbens (Nac) and ventral tegmental area. Finally, to evaluate neurochemical changes induced by administration of these drugs we performed an in vivo microdialysis. Interestingly, our results showed that TEMPOL (I.P; 100 mg/kg) attenuates the increase of DA induced by AMPH (Intra-probe;100 um) in Nac. Taking together, our results strengthen the idea that ROS modulate locomotor and reinforcing effects induced by psychostimulants.

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amphetamine, dopamine, oxidative stress

Altered excitability in olfactory cortex layer II neurons in Fmr1 KO mice

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Fragile X syndrome (FXS) is the first genetic cause of autistic spectrum disorders and the first cause of inherited mental retardation in men. This syndrome is caused by a mutation in the FMR1 gene in chromosome X that causes its silencing by hypermetilation and thus the absence of the FMR protein (FMRP) expression. FMRP is ubiquitously expressed through the nervous system, acting as a translation repressor and activity modulator of several proteins involved in key neuronal processes. A feature of FXS symptomatology is hyperreactivity to sensory stimuli, including olfaction, and proneness to epileptic seizures, suggesting an altered neuronal excitability phenotype in FXS neuronal networks. Behavioral data from our lab using the Fmr1 KO mice, a murine model of FXS, shows they have a higher threshold for odor detection and an incapacity to discriminate between similar complex odor mixtures. The anterior piriform cortex (aPC) is critical for adequate olfactory processing and odor discrimination, thus we propose to investigate this region in Fmr1 KO mice. Here, we used brain slices patch-clamp recordings to assess neuronal excitability and intrinsic membrane properties of neurons in layer II of the aPC of wildtype (WT) and Fmr1 KO mice. Our preliminary data shows these neurons in the Fmr1 KO mice have lower input resistance, higher membrane capacitance and a more hyperpolarized resting potential compared to WT animals. These results suggest that the network exhibits an altered neuronal excitability profile that could play a role in the olfactory behaviors disfunctions observed in the Fmr1 KO mice.

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Olfactory disfunction, Whole-cell pacth-clamp, Neuronal excitability

Glucagon modulates the inhibitory activity of mouse retinal rod bipolar cells in a dopamine D1 receptor-dependent manner

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Myopia is the most common refractive error in the world, characterized by blurry vision of distant objects, and has experienced a marked increase in its worldwide prevalence during the last decades. Glucagon is a molecule known for its role regulating glycaemia, but it is also involved in the development of myopia, working as a protective counter agent. In chicken, glucagon has been shown to be associated with a subgroup of amacrine cells sensitive to the sign of image defocus, which may put this molecule at the beginning of myopia development. On the other hand, dopamine is the most studied neuromodulator related to myopia, and has been proposed as the signal regulating eye growth, antagonizing myopia. Despite the importance of both signals in myopia pathogenesis, no studies so far addressed a possible interaction between them. Here, we test this putative interaction by measuring the effects of glucagon on rod bipolar cell inhibitory input, which is modulated by dopamine. Using patch-clamp recordings in mouse rod bipolar cells, a model animal closer to primates, we have found that glucagon increases the frequency and amplitude of IPSCs, and that this phenomenon is dependent on dopamine D1 receptor activation. Using calcium imaging, we found a subpopulation of cells exhibiting responses to glucagon, with two amacrine cell types showing an increase and a bipolar cell type showing a decrease. Further experiments are projected to better understand the signaling pathway and to determine if this mechanism is involved in myopia development using a mouse myopia model.

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retina, glucagon, dopamine

Using 3D convex hulls to analyze the intersection between dopamine neurons receptive domains

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Overlap between dendritic trees of neighboring neurons is a defining feature of the nervous system and its study is relevant to define, among other phenomena, the redundancy of nervous units and topography of circuits. In sensory organs, overlap between dendritic or terminal fields has been studied using convex hull (CH) polygons. However, CH polygons are limited to two-dimensional fields, and therefore not suitable to study the three-dimensional domain of spatially complex neurons. We developed a method to analyze the shared receptive domain of central neurons using three-dimensional CH polyhedrons (CHP) . Sets of reconstructed dopaminergic neurons from substantia nigra pars compacta (SNc) and ventral tegmental Area (VTA) were used. CHP of neurons were obtained and then the intersection ratio (IR) between pairs of CHP was quantified using Matlab scripts. Then, we modeled the influence of distance, volume and shape of neurons in the IR of SNc and VTA neurons. Our results indicate an expected, albeit complex, effect of position, volume and shape between pairs of CHP. Our data also suggest that a specific pattern of intersection of receptive domains can be a feature that distinguishes SNc from VTA neurons.

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Dopamine neurons, Convex Hull, Neuroanatomy

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

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Background: The pathophysiology of depression is associated with dysregulation of glutamate system and clearance mechanisms in brain regions mediating cognitive-emotional behaviors. However, the mechanisms underlying the abnormal glutamatergic transmission in depression remain controversial.Aims: To evaluate the consequences of unpredictable chronic mild stress (UCMS) on the expression of glutamate transporters and receptors in cortical-limbic areas in wild type (WT) mice.To determine if increased EAAT3 expression in the forebrain in mice can reduce susceptibility to UCMS.Methods: WT mice subjected to UCMS and control group were tested to anxiety and depressive-like behaviors. Protein levels of AMPA and NMDA receptor subunits and glutamate transporters were analyzed by western blot.Mice with EAAT3 overexpression driven by CaMKIIα-promoter (EAAT3glo/CMKII) and control (EAAT3glo) littermates were assessed to anxiety and depressive-like behaviors in baseline and UCMS conditions.Results: UCMS increased EAAT1, NMDA GluN2A and GluN2B subunits, and AMPA GluR1 subunit protein levels in the hippocampus in WT mice. Similar alterations in NMDA GluN2B subunit protein levels were also found in the medial prefrontal cortex. Furthermore, in baseline conditions EAAT3glo/CMKII mice showed anxiety-like behavior in open field test and lower despair behavior in tail suspension test. However, UCMS did not increase immobility time or trigger anhedonia in EAAT3glo/CMKII mice.Conclusions: Hippocampal glutamatergic system alterations may underlie the depressive-like behaviors. Moreover, we suggest that EAAT3 overexpression in the forebrain in mice may be linked to a resilient phenotype to chronic stress.

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Depression, stress, glutamate

Neuron dynamic of the medial prefrontal cortex associated with compulsive alcohol seeking. (Dinámica neuronal de la corteza prefrontal medial asociada a la búsqueda compulsiva de alcohol.)

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Previous studies on cocaine addiction have proposed the presence of a ventral/dorsal functional dichotomy in the medial prefrontal cortex (mPFC), which through its projections from the prelimbic area (PL) towards the nucleus accumbens (NAc) core would guide drug-seeking behaviors, while, projections from the infralimbic area (IL) towards the NAc shell, would guide the extinction behaviors. As dependence progresses, motivation for alcohol increases in intensity, however, it is unknown how the neural dynamics of these regions change in the transition to dependence. One of the components that characterize the development of dependence is compulsive alcohol seeking, which can reflect a high motivation for a substance or the inability to extinguish a behavior. Using operant conditioning tasks we analyzed the neuronal dynamics of mPFC associated with motivation for alcohol intake, in alcoholic rats line (UChB), following short-term (Acute Condition) versus long-term (Chronic Condition) alcohol consumption. Long-term consumption for 45 days (Chronic Condition) increases the motivation for alcohol, reaching a higher breaking point during the progressive ratio task. The behavioral differences were associated with the neuronal recruitment of assembles with anticipatory activity in the prelimbic cortex. These results give us new ideas about the changes in the prefrontal neuronal activity which could explain the compulsive behavior during addiction in rodents.

Alcohol Seeking, Medial Prefrontal Cortex, Single-Unit Recording

Impact of sleep on incubation of cocaine craving and dopamine terminal adaptations following cocaine abstinence (Impacto del trastorno de sueño en la incubación del deseo por consumir cocaína y cambios en las terminales dopaminérgicas durante la abstinencia.)

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Finding effective and tolerable treatments for cocaine addiction has been extremely challenging due to the high rates of relapse. Clinical and animal studies have shown a progressive intensification of cocaine seeking and craving during abstinence, increasing the likelihood of relapse. In addition, sleep disruptions are commonly observed during recovery from chronic cocaine use and manifest as abnormal sleep architecture which is posited to promote incubation of cocaine craving. While the neural mechanisms underlying the association between sleep disruption and incubation of cocaine craving are unclear, accumulating evidence suggests that alterations in mesolimbic dopamine (DA) neurotransmission may contribute to these processes. To address this issue male and female rats underwent intermittent access cocaine self-administration, a recently designed self-administration schedule that mimics binge-like patterns of consumption usually observed in humans, followed by a period of imposed abstinence to engender sleep disruptions. I then test whether restoring sleep during abstinence prevents incubation of cocaine craving via normalization of DA terminal function in the nucleus accumbens. Intermittent access to cocaine followed by abstinence engenders a significant decrease in sleep. However, restoring sleep during cocaine abstinence attenuates incubation of cocaine craving and DA terminal adaptations. These results suggest that sleep disruptions might not only be a symptom but also an important factor promoting incubation of cocaine craving.

Drexel University Dean's Fellowship for Excellence in Collaborative Research (IPA) NIH DA031900 (RAE) Dopamina, cocaína, sueño

N-acetylcysteine prevents spatial memory deficits and the enhanced redox-dependent RyR activity displayed by aged rats

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Aging often entails impaired hippocampal synaptic transmission and plasticity -which correlate with learning and memory impairments– and increased neuronal generation of reactive oxygen species (ROS). We have reported previously that ROS increases calcium release via ER-resident ryanodine receptor (RyR) channels in the hippocampus. These RyR channels are oxidized in aged rats, generating anomalous calcium signals. Previous evidence suggests that the antioxidant N-acetyl-cysteine (NAC) protects the brain against redox-induced damage. Accordingly, we tested the effects of NAC treatment on learning and memory and neuronal RyR activity on aged and young rodents. We used aged rats (22 months old; control and NAC-fed) and young rats (3 months old; control and NAC-fed). NAC feeding was performed for 3 weeks before testing. To evaluate spatial learning and memory, animals were trained during 6 days in the Oasis Maze, which involved searching for a reward in 1 of 21 equidistant wells on a circular arena. All sessions were video-recorded and analyzed using a Matlab routine. The hippocampus was dissected, and ER-enriched fractions were isolated to evaluate RyR single-channel activity in lipid bilayers. Compared to control aged rats, NAC-fed aged rats exhibited improved performance in learning and memory and displayed a higher fraction of reduced (low activity) and a lower fraction of oxidized (high activity) RyR channels. Based on these results, we suggest that excessive RyR-mediated calcium release induced by oxidation contributes to impair spatial memory processes in aged rats and that NAC treatment, by reinstating redox balance, improves hippocampal memory and restores normal RyR activity.

BNI-P-09-015F, FONDECYT (1170053) Aging, Calcium, Hippocampus

Pupil dilation as a marker of awareness of unperformed saccades. (Dilatación pupilar como marcador de conciencia de movimientos sacádicos no realizados.)

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Every day, we are exposed to different visual stimuli, which trigger a change in our pupil size. Previous studies in cover attention tasks suggest that pupil dilation changes reflect our attentional focus and occur when we attend peripheral stimuli without directing our gaze. Also, pupil dilation has shown to reflect a motor preparation for a saccadic movement, even before a saccadic movement was performed. In previous experiments, we observed some participants reported moving their eyes when, in fact, further analysis revealed they did not perform any saccadic movement. In this context, the question arises as to whether pupillary dilation acts as a marker for this sensation of having performed saccades.To evaluate this, we analyzed data from a covert attention task focused on the participants' self-reported eye movement perception. Pupil size from thirty subjects (19 to 34 years old) were recorded through video-oculography while they recognize facial emotions from pictures presented extrafoveally. In case of perceiving eye movements outside the fixation cross, participants had to report them pressing a button. Participants were unaware of the real purpose of the study. Pupillary dilation changes were analyzed before and after: a) a report of an unperformed saccadic movement, b) an unreported saccade, and c) a report of a performed saccadic movement. The results indicate that pupil size changes before and after a report and before and after a saccade. Our findings suggest the pupillary dilation reflects an attentional shift instead of a saccadic movement.

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Pupil dilation, Awareness, Covert Attention

Use of different spatial navigation strategies in a virtual Environment in controls and Mild Cognitive Impairment patients. (Uso diferencial de estrategias de navegación en ambientes virtuales en controles versus pacientes con deterioro cognitivo leve.)

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Amnestic mild cognitive impairment (aMCI) is considered an intermediate cognitive stage between normal aging and Alzheimer's disease and it can course with deficits in spatial navigation. However, it is not known whether this worse performance is due to a quantitative deficit or refers to differential use of strategies in spatial navigation. To answer this question 41 young subjects, 20 healthy older adults, and 18 patients with aMCI, were tested in a Virtual Morris Water Maze spatial navigation task of increasing difficulty. Then typically variables to assay learning were analyzed such as latency, success rate, and traveled distance, as well as non-classical learning parameters mostly associated with navigation strategies such as different error entropies, distance to the center of the maze, straightness. In learning parameters, both young people and healthy older showed progress and better yields than patients with aMCI. In turn, it is was found that the three groups occupy different strategies of navigation to reach the platform on the maze, suggesting that the natural cognitive decrease associated with aging could be distinguished from the pathological condition by using this kind of technology.

Instituto de Neurociencias Biomédicas (BNI), ICN09_015 Human Spatial Navigation, Mild Cognitive Impairment, Virtual Spatial Navigation

Heart rate variability changes during virtual spatial navigation in humans. Major autonomic responder, better learners?

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The autonomic tone is a balance between the sympathetic and parasympathetic systems to keep our homeostasis constant. This balance is regulated by the central autonomic network, involving bidirectional connections between the interoceptive system and other higher cognitive centers. Even though it has been demonstrated that autonomic tone is a critical predictor of adaptive cognitive success, all this has been proved in the prefrontal cortex demanding tasks, such as working memory or inhibitory control. Therefore, the relationship between the autonomic nervous system and hippocampus-dependent spatial memory has not been explored. The main objective was to establish the occurrence of changes in the autonomic tone - measured through heart rate variability (HRV) and frequency (HF) - during the execution of a virtual spatial navigation task in healthy humans, to define any relationship between this cognitive ability and changes in the autonomic response. For this purpose, 42 healthy young subjects (17-23 years old) were tested during a spatial navigation memory task by using the Virtual Morris Water Maze with two different degrees of difficulty, while the heartbeat was recorded with a wireless monitor. Our results show consistent spatial learning in the behavioral task since hit rate, latency, and traveled distance to the target improved with the progression of the task. The improvement in spatial learning was paralleled with changes in HRV but not with HR variations, suggesting that during learning, and proportional to the degree of cognitive load, a predominant parasympathetic component is relevant for spatial learning.

Heart rate variability, Virtual spatial navigation, Spatial memory

Influence of Negative Symptoms on Social Cognition in patients with Schizophrenia (Influencia de los Síntomas Negativos sobre la Cognición Social en pacientes con Esquizofrenia)

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Introducción: La esquizofrenia (EQZ) es un trastorno psiquiátrico de carácter grave de curso invalidante. Los síntomas positivos, negativos y cognitivos generan un deterioro importante en la funcionalidad si no existe una adecuada intervención y tratamiento. Dentro de la sintomatología se suma el deterioro de la cognición social (CS).Objetivo: El estudio se basó en la caracterización de síntomas negativos en personas con esquizofrenia y su influencia sobre la cognición social.Método: Estudio comparativo-correlacional, grupo EQZ n=9, grupo control n=15, todos >18 años. Ambos grupos evaluados mediante: Escala de conducta de Cambridge, Reading the Mind in the Eyes, Reconocimiento Emocional en Caras, Faux-Pass, MoCA y PANSS- Escala Negativa.Resultados: Existen diferencias significativas entre ambos grupos en las tareas de cognición social tales como Reading the Mind in the Eyes, Reconocimiento Emocional en Caras y Faux-Pass, U Mann-Whitney ($p<0.05$). En el rendimiento cognitivo global evaluado con MoCA existen diferencias significativas U Mann-Withney ($p<0.05$). En la escala clínica, PANSS-Escala negativa U Mann Whitney ($p<0.05$). Se realizó análisis de correlación de Spearman ($p>0.005$) entre síntomas negativos y cognición social. Conclusión: No existe una relación entre los síntomas negativos de EQZ y el rendimiento en cognición social. Existen diferencias en el rendimiento en cognición social, sobre todo en reconocimiento facial de emociones y teoría de la mente, entre sujetos EQZ y controles. Estas diferencias se asocian con la baja funcionalidad social que se reporta en EQZ.

Síntomas negativos, Cognición social, Esquizofrenia

Magnocellular deficits and facial emotions recognition in subjects at clinical high risk of psychosis

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Background: La esquizofrenia se caracteriza por presentar deficiencias en el procesamiento sensorial, cognitivo y en cognición social. Durante los ultimos años, estos mismos deficits se han reportado en pacientes con estados mentales de riesgo de psicosis (EMARs). El objetivo de este trabajo es determinar si existe un deficit en el procesamiento visual durante la realización de tareas de cognición social en sujetos EMARS y si estas alteraciones son magno o parvocelulares. Metodo: Dos grupos de estudio, grupo EMARs n=7, grupo control n=16. Evaluados con Structured Interview for Prodromal Symptoms (SIPS). MATRICS para rendimiento cognitivo. Y una tarea de reconocimiento facial de emociones (Penn emotion recognition PERT-96) a la que se aplicaron filtros de alta (HSF) y baja frecuencia espacial (LSF), para determinar alteraciones parvo o magnocelulares. Para esto se obtuvieron ERPs con EEG biosemi 64 canales. Resultados: No existen diferencias significativas en peak de amplitud de componentes N170 y N250 asociados a reconocimiento facial de emociones. Existe correlación entre numero de aciertos en respuestas de reconocimiento facial de emociones y teoría de la mente, con el puntaje en escalas de sintomas positivos, solo con estimulos LSF (parvocelulares). Esto no ocurre con estimulos HSF. Conclusiones: No hay datos concluyentes para afirmar que existe una diferencia en el procesamiento visual de estimulos LSF y HSF en sujetos EMARS. Conductualmente existe una relación clinica interesante entre la presencia de sintomas positivos psicoticos cuando se presentan estimulos LSF durante el reconocimiento de emociones, esto confirma parcialmente la hipotesis de alteraciones magnocelulares en sujetos EMARS.

social cognition, clinical high risk psychosis

Oscillatory responses during imitation-inhibition and its impact on the sense of agency. (Respuestas oscilatorias durante la imitación-inhibición y su impacto en el sentido de agencia)

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An emergent literature suggests that sensorimotor processes are important for the sense of agency, the experience that we can control our actions and its effects in our surrounding. In a previous study the imitation-inhibition paradigm was used to demonstrate that performing actions while observing compatible relative to incompatible actions led to an increased implicit sense of agency. Here, we used electroencephalography to investigate the spectrotemporal dynamics associated with imitation-inhibition task and we further explored its possible links with the sense of agency. We administrated participants the imitation-inhibition task coupled to an intentional binding assessment, an implicit measure of the sense of agency. We replicated previous behavioural results with compatible relative to incompatible actions leading to greater intentional binding. At the neural level we found decreased alpha and beta power for compatible relative to incompatible actions and increased gamma and theta power for incompatible relative to compatible actions. A specific brain-behaviour correlation suggest a relationship between intentional binding and gamma power oscillations. Our study shed new light regarding the spectrotemporal organization associated with automatic imitation and suggest that cognitive interference might contribute to changes in the sense of agency in the imitation-inhibition task.

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sense of agency, neural oscillations, automatic imitation

Structural features define the best targets for changing whole-brain dynamics via neuromodulation (Las características estructurales señalan los mejores blancos para cambiar la dinámica cerebral por medio de la neuromodulación)

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Brain structural connectivity has small-world properties, allowing the coexistence of segregated and integrated states of brain activity. However, the human connectome is essentially static, and neuromodulatory systems facilitate the transition between different brain states. Recent computational studies have shown how an interplay between the noradrenergic and cholinergic systems define these transitions, but these models consider a homogeneous effect of a neuromodulator on the network. In order to understand better the relationship between structural connectivity features and neuromodulation we used a whole-brain model, based on the Jasen & Rit equations, to find out which structural features of the human connectome network define the best neuromodulatory targets to promote the integration-segregation shift. We simulated the effect of noradrenergic and cholinergic systems as changes to neural responses, inhibitory feedback and neural gain. First, we found that the ability of the network of transiting through a variety of dynamical states depends heavily on the distribution of connection weights and delays. Then, we simulated neuromodulation only on an increasing subset of the network nodes, selected according to distinct structural network features. We found that the nodes belonging to rich club and those that have a high participation coefficient are the ones that most effectively can alter the dynamics of the network. Overall, our findings clarify how the network spatial and temporal features, at macro and meso-scale levels, interact with neuromodulation to facilitate the switching from segregated to integrated brain states and to sustain a richer brain dynamics.

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Neuromodulation, Whole-Brain Modelling, Structural Connectivity

Study of individualized co-expression networks and their application in the stratification of transcriptomic data related to neuronal cell types and neurodegenerative diseases

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Personalized medicine aims to elucidate the specific molecular mechanisms causing disease affected in each individual. Importantly, diseases generally result from dysfunction at the network level, instead of the malfunction of single components. At the genomic level, this is usually studied knowing the correlation between the expression of different genes in samples, commonly represented as co-expression networks. Traditional co-expression networks show averages among samples and, as a disadvantage, they erase the heterogeneity of each individual or sample. However, personalized co-expression networks help to stratify different groups within a population into subtypes, allowing them to know what is happening at the molecular level in each sample. We have evaluated different methods for the generation of personalized networks. These methods are based on measures of dependency or correlation in multidimensional datasets. To evaluate conventional and personalized co-expression strategies, first, we study expression changes in cell populations, to study changes in molecular functions of glutamatergic and gabaergic neurons, and second, we simulated data to reproduce different gene expression patterns within a population, to perform stratification of datasets.We determine differentiated networks and molecular processes for each cell type and we identify which method is best in terms of sensitivity, specificity, and precision. Thus, we have established the means to reliably determine which approach is best to stratify cells or simulated data.

Automatic features extraction for retinal ganglion cells from a vertebrate retina using frequency modulation stimulus.

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The retina is a multilayer structure able to transform a luminous signal into an electrical signal through retinal ganglion cells (RGCs). Retinal Ganglion Cells (RGCs) transform the electrical activity into action potentials encoding the information to be processed in the brain. Chirp stimulus (CS) is a multistimulus capable of stimulating the retina in many different manners, such as flashes, amplitude, and frequency modulation, allowing us to extract and classify RGCs from a large population. Here we use data already collected in the lab and we developed a new semi-automatic method, to analyze frequency modulation in CS to classify different RGCs responses. The frequency modulation of CS constitutes increasing linear frequency from 0 to 15 Hz in 15 s, where RGCs responded (from Octodon degus retina) in a series of spike events, recorded in a 252 multielectrode array. First of all, we computed spike frequency (using a 60 ms Hann moving window) and peak frequency (detection above a noise threshold, defined as two mean frequency), as well as On and Off labeling. Then we obtained seven parameters: 3 parameters were obtained using a Gaussian fitting i) central frequency (f0), ii) frequency standard deviation (sigma), iii) maximal spike frequency (fmax), 2 parameters were shortest stimulus-response (delay) and maximal chirp frequency reached by the response (fcut) and 2 quality parameters signal to noise ratio (SNR in dB) and RMSE (root mean square error) between fit and experimental spike frequencies. The approach was successfully applied to different experiments.

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Octodon degus, retinal ganglion cells, chirp stimulus

Non-Invasive Modulation of Stress Resilience During Prepuberty and Adulthood in Rats

(Modulación no invasiva de la resiliencia al estrés durante la prepubertad y adultez en ratas)

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Stress resilience is the ability to adapt quickly to adversity. When stress resilience decreases, the brain's vulnerability to neuropsychiatric disorders increases. The aim of this study was to evaluate two non-invasive methods to promote stress resilience during prepuberty and adulthood in Sprague Dawley rats. First, we determine whether enhances maternal care (early handling) can counteract the effects of prenatal stress during prepuberty. Plasma corticosterone levels was quantified as stress marker. Glucocorticoid receptor (GR) levels in the amygdala and hippocampus, as well anxiety- and depressive-like behaviors were assessed. Second, we investigate whether daily stroking, specifically targeted to activate a velocity/force tuned class of low-threshold c-fiber mechanoreceptor (CLTM), confers resilience against established markers of chronic unpredictable mild stress (CMS). Adult male rats were exposed to CMS protocol. Throughout the CMS protocol, some rats were stroked daily, either at CLTM optimal velocity (5cm/s) or outside the CLTM optimal range (30cm/s). The effect of CMS on plasma corticosterone levels, anxiety- and depressive-like behaviors in these groups were assessed in comparison to non-CMS exposed rats. Gestational stress increased levels of stress markers, anxiety- and depressive-like behavior in prepuberal rats, these effects were stronger in males and countered by early handling. In adulthood, CLTM optimal velocity stroking did significantly reduce CMS induced elevations in corticosterone following an acute forced-swim. Rats receiving CLTM optimal stroking also showed significantly fewer anxiety-and depressive-like behaviors than non-stressed rats. Together, these findings support the theory that stress resilience can be non-invasively modulated during childhood and adulthood.

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Orgasm's emotion: Neurophysiological response to sexual pleasure's facial expression perception (La emoción del Orgasmo: Respuesta neurofisiológica a la percepción de expresiones faciales de placer sexual)

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Facial expressions of basic emotions are thought to be universal and their recognition might be culture-independent. Facial expressions communicate emotional states. Likewise, it is thought that orgasm's expression also has a communicative function. Despite knowledge about facial expressions and their neural correlates (e.g electroencephalographic (EEG) N170 component) little is known about the orgasm's facial expression perception. Here we compared N170 evoked by basic emotion facial expressions to waveforms evoked by orgasm's expressions. Experiment 1: A novel stimuli set (orgasm, happy, anger, pain, eyes up, eyes down, and neutral) was created and validated. 255 participants attributed emotional states to the images and assessed expression intensity. Experiment 2: 19 participants attributed valence to images of Orgasm, Happiness, Anger, and Neutral facial expressions with 0, 20, 40, 60 and 80% noise while measuring EEG. Experiment 1: Successful validation of stimuli set. Experiment 2: N170 evoked component was analyzed. Amplitude to Orgasm faces was similar to Happiness and Anger. Orgasm faces showed longer latencies compared to Happiness and Neutral faces. Image noise levels attenuated P1/N170 peaks. Results show that the N170 EEG component peak amplitude evoked by Orgasm faces is equivalent to other emotional facial expressions with a small latency increment. We interpret that orgasms faces are processed similarly to other emotion facial expressions.

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Orgasmo, Emociones, N170

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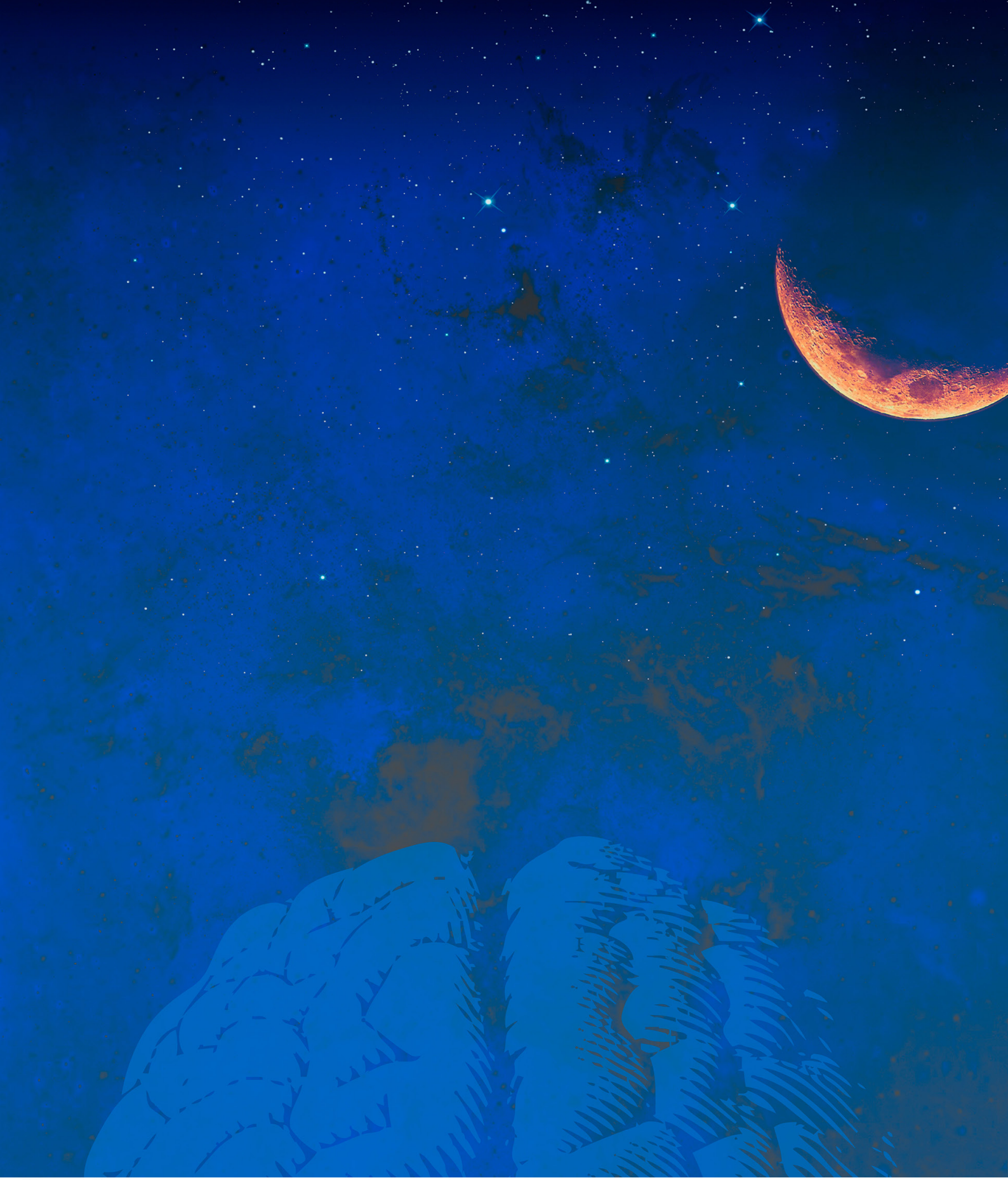

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