

Sociedad Chilena de Neurociencia

XXI REUNIÓN ANUAL

Libro de resúmenes

Campus de Isla Teja
Universidad Austral, Valdivia
1 al 3 de octubre de 2025.

2025

WEDNESDAY	THURSDAY	FRIDAY
REGISTRATION	**S2:** Mechanisms of Brain Dynamics: Multiscale Computational Models and Translational Insights *Chair: Dr. Vicente Medel*	**S4:** Decoding Fear Memories Outside the Box *Chair: Dr. Alexies Dagnino*
	Coffee Break	Coffee Break
S1: Neurodevelopmental Disorders: A Cellular and Systemic Perspective *Chairs: Dr. Alexia Nunez-Parra and Dr. Patricio Rojas*	**S3:** Huellas en el Camino Neurocientífico de la Dra. Katia Gysling: Su Impacto en Chile y el Mundo *Chair: Dr. Paola Haeger*	**S5:** Fueling the Mind: The Role of Energy Metabolism in Neural Learning and Behavior *Chair: Dr. Pedro Maldonado*
Break	Break	Break / Reunión de socios
Poster Session I & Coffee	Poster Session II & Coffee	Oral Comunication I & Oral Comunication II
Bienvenida Ceremonia de Premiación Becas SCN-IBRO	Young Neuroscientists Symposium (YNS) *Chair: Dr. Evelyn Avilés*	Plenary Lecture Dr. Diego Restrepo *Chair: Dr. Alexia Nunez-Parra*
Conferencia Mario Luxoro Dra. Úrsula Wyneken		Ceremonia Premiación Mejor Póster y Comunicación Oral
WELCOME COCKTAIL	Plenary Lecture Dr. María Eugenia Pedreira *Chair: Dr. María Pertusa*	

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Chronicle of a stress foretold: Flowing from
to astrocytes and the systemic adaptations
disorders


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PLENARY LECTURES

Chronicle of a stress foretold: Flowing from glutamate to astrocytes and the systemic adaptations to mood disorders

Ursula Wyneken[1]

(1) Centro de Investigación e Innovación en Biomedicina, Universidad de los Andes; IMPACT, Center of Interventional Medicine for Precision and Advanced Cellular Therapy

The astonishing complexity of brain function encompasses at the very least genes to synapses, neurons and glial cells impacting on behaviorally relevant brain circuits. During my scientific journey, we contributed to describe the fine molecular make up of glutamatergic synapses, the most abundant of our nervous system. Thus, we electro physiologically revealed glutamate receptor functioning in single post-synaptic densities. When all mood disorders seemed to be rooted in monoaminergic pathways, we explored the other way round and rather focused on long-term plastic excitatory adaptations. As such, we described the consequences on glutamaterigc neurotransmission and behavior of chronic antidepressant treatment with fluoxetine (primarily targeting serotonin re-uptake). Aimed at understanding the underlying neurobiology of mood disorders, our lab performed different proteomic strategies to reveal neuronal brain adaptations during stress and antidepressant treatments. Unexpectedly, astrocytes got on our pathway. Indeed, analyzed brain fractions revealed that aldolaseC, an astrocytic glycolytic enzyme, was largely regulated by stress and antidepressant treatments. By performing brain in utero electroporation we identified its presence inside extracellular vesicles (EVs) secreted by astrocytes, which turned out to be “exported” to neurons and the blood stream. Notably, in the bloodstream, these vesicles may target different body organs impacting the gut’s immune function. This emerging scenario opens at least two questions 1) How do brain-EVs target body organs and regulate their function? 2) Can the highly heterogenous molecular cargo of EVs be used to reveal specific brain disorders? These exciting questions are very likely the beginning of unimaginable beautiful research destiny.

Updating declarative and aversive memories: from a behavioral approach to neural signatures of reactivation using EEG.

Maria Eugenia Pedreira[1]

(1) Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE, UBA/ CONICET), Laboratorio de Neurociencias de la memoria, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Av. Costanera Rafael Obligado, Ciudad Universitaria, Ciudad Autónoma de Buenos Aires, (C1428EGA), Argentina

Memory updating is crucial for adaptability in both humans and animals, as it enables adjustments of behavior in a continuously changing world. Declarative memories allow us to recall facts and experiences, showcasing memory's flexibility, while threat learning results in implicit memories that prompt defensive behaviors. Despite their differences, both types of memory involve reactivation and change, helping us understand adaptation and the potential for maladaptive conditions like anxiety or PTSD. Intriguingly, the mechanisms governing memory malleability are not yet fully described. Nowadays, it is acknowledged that external cues trigger memory reactivation. This reactivation has been proposed to mediate memory malleability, promoting the opening of a time window for changes in the original memory trace. Prediction error, the incongruence between what was learned and what occurs, plays a pivotal role in memory updating. We have demonstrated that the impact of a reminder cue, along with the characteristics of the original memory, can lead to selective changes such as strengthening, weakening, or updating of the memory. From here, we aim to explore the brain oscillation signatures that underpin cognitive and behavioral processes. In this presentation, I will outline our research journey, employing a behavioral approach, into two types of memories: declarative and aversive memories. Then, I will share experiments designed to investigate the neural activity elicited by reminders with prediction error, examining resting states before and after the reminder presentation. These experiments mark a significant step forward and raise new questions about the conditions that facilitate memory updating.

Funding: MEMORIAS AUTOBIOGRÁFICAS: correlatos neurales de su acceso, elaboración y su modificación por el proceso de reconsolidación. (conicet).

Neural Circuits in Olfactory Decision-Making, Learning, and Memory

Diego Restrepo[1]

(1) University of Colorado Anschutz Medical Campus, Cell and Developmental Biology, School of Medicine, Aurora, Colorado, USA

The dorsal CA1 (dCA1) region of the hippocampus underlies learning and memory via highly organized cellular and circuit mechanisms that encode spatial, temporal, sensory, and behavioral variables. While dCA1 is established in spatial and episodic representation, its importance in olfactory associative learning—specifically linking odor events to valence and context—remains disputed, as lesion studies suggest predominant roles for the piriform cortex and amygdala in the go-no go olfactory associative learning task. New data from our laboratory indicate that dCA1 pyramidal cells encode odorant valence in go-no go paradigms, with multiphoton calcium imaging showing activity patterns reflecting rewarded versus nonrewarded odorants in thirsty mice. In addition, we have characterized responses of pyramidal cells in dCA1 when mice navigate an arena in the presence of odor plumes, an ethologically relevant odor task. In miniscope recordings in freely behaving mice we find that that dCA1 ensembles encode mean odor concentration during odor plume navigation, with distinct neuronal populations predictive for location or odor concentration. Finally, I will discuss ongoing research implicating viral infection as a mechanism driving early olfactory loss in Alzheimer’s disease.

Funding: NIH R01AG079193

SYMPOSIA

SYMPOSIUM 1

Altered synaptic plasticity in the dentate gyrus in an animal model of autism

Chairs: Alexia Nunez-Parra and Patricio Rojas

Patricio Rojas[1]

(1) Universidad de Santiago de Chile, Departamento de Biología, Facultad de Química y Biología, Santiago, Chile

A neurodevelopmental disorder, autism spectrum disorder (ASD) is defined by sustained limitations in social communication and interaction, and by stereotyped forms of behavior, interests, or activities. An elevated excitationinhibition ratio has been documented across multiple areas as the hippocampus, a structure critically involved in spatial orientation, episodic recall, and emotional regulation. A crucial stage in development involves the alteration in GABA's influence, transitioning from excitatory to inhibitory. Animal models of autism exhibit a delayed "chloride switch", linked to intracellular chloride, which is mantained by the activity of the Na+K+Cl- cotransporter 1 (NKCC1). In this work we studied the participation of NKCC1 on synaptic plasticity in the dentate gyrus of the valproate (VPA) model of autism, a region that acts as a filter of information from cortical inputs. We observe the existence of a NKCC1- dependent component of EPSP which is higher in VPA group. Both AMPA and NMDA components of EPSP are dependent on NKCC1 activity. The application of four high frecuency stimulation pulses induced a robust LTP, which has a presynaptic component due to presynaptic mechanisms. Animals exposed to VPA displayed enhanced LTP levels in contrast to the control group, whereas the external application of bumetanide reverted these levels to those characteristic of control animals, implying NKCC1's contribution to this augmented plasticity. Altogether, our results suggest that in the VPA model both the size of EPSP and the induction of LTP depends on the activity of NKCC1 cotransporter, potentially due to a depolarizing or even excitatory effect of GABA.

Funding: Funded by DICYT-USACH 022343RM.

Social Cues coding in a mouse model of Fragile X Syndrome

Alexia Francisca Nunez-Parra[1]

(1) Universidad de Chile, Department of Biology, Faculty of Science, Chile

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and a major genetic contributor to autism spectrum disorder. Individuals with FXS consistently exhibit profound social behavior deficits and atypical sensory processing, yet the neural mechanisms linking these domains remain poorly understood. In rodents, social behaviors are orchestrated by complex neuronal circuits that process chemosensory cues found in bodily fluids such as urine.
These cues are detected by sensory neurons located in the vomeronasal organ whose axons project to the accessory olfactory bulb (AOB), where initial processing occurs. The principal neurons in the AOB, the mitral cells (MC), project directly to cortical and limbic structures Little is known, however, about how Fmr1 KO mice process social cues.

By integrating behavioral, anatomical, and electrophysiological analyses, this research aimed to uncover how deficits in social cue discrimination and sociability in Frm1 KO mice are correlated with AOB circuitry disruptions. We found that KO detect but cannot discriminate conspecific social cues, failed to distinguish between familiar and unfamiliar individuals. Moreover, we found that they showed reduced glomerular layer volume in the anterior and that their projection neurons exhibited increased dendritic branching compared to WT mitral cells. Supporting this, whole-cell patch-clamp recordings revealed altered intrinsic properties in KO mitral cells including longer slower action potentials and reduced excitability. Together, these findings suggest that Frm1 deletion compromises AOB circuitry in a way that selectively affects social information processing, offering a mechanistic link between sensory discrimination deficits and altered social behavior.

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

Congenital hydrocephalus: a pathology of neural stem cells

Montserrat Guerra[1]

(1) Universidad Austral de Chile, Instituto de Anatomía, Histología y Patología, Facultad de Medicina, Valdivia, Chile

Introduction Congenital hydrocephalus is one of the most challenging paediatric diseases. Neurological impairment (sensory, motor, memory and learning deficits) of neonates with congenital hydrocephalus is not reversed by cerebrospinal fluid (CSF) derivative surgery. **Goals** Through the present investigation we have explored the ethiopathological process leading to hydrocephalus to explore new therapeutical approaches for children born with congenital hydrocephalus. **Methods** The brain of hydrocephalic hyh mice, HTx rats, and hydrocephalic human foetuses, were processed by optical and electron microscopy at different gestational stages, and they were further studied by using immunohistochemical procedures. Antibodies against Nestin (neural stem cells), GFAP (astrocytes), B3-tubulin (neural progenitor), and B4-tubulin (ependyma) were used as cell markers. The expression of cell junction proteins (N-cadherin and connexins) was also studied. **Results and Discussion** Abnormal expression of cell junction proteins in neural stem cells/ependyma appears as a final common pathway of the ethiopathological process leading to congenital hydrocephalus and outcomes: abnormal brain development and neural impairment. It stimulated us to explore a cell therapy based on the early grafting of neural stem cells into the CSF of hydrocephalic HTx rats. It resulted in the partial reparation of the germinal matrix and the improvement of specific neural functions, as assayed by using standardized neurological and cognitive tests (NOR test). These results open a new avenue for the treatment of congenital hydrocephalus as the culmination of a persistent research effort and the convergence of interdisciplinary capabilities at the University Austral de Chile and foreign associated laboratories.

Funding: Grant: MUJ-INV-2023-03 (UACh)

Oscillatory Activity and Social Development in Autism: From Joint Attention to Theory of Mind.

Patricia Soto-Icaza[1]

(1) Universidad del Desarrollo, Laboratorio de Neurociencia Social y Neuromodulación, Centro de Investigación en Complejidad Social (CICS), Facultad de Gobierno, Av. Las Condes 12.461, oficina 307, Edificio 3, Santiago, Chile

Autistic children often face challenges in social contexts, yet the neural correlates of these challenges and their specific role in the development of social cognition remain unclear. We examined how neural oscillations support the progression from early social skills to complex mentalizing abilities, and how these dynamics differ between autistic and non-autistic children. In previous work, we studied joint attention (JA) as an early social-communicative skill involving sharing attention on an object with another person, which precedes the development of the capacity to attribute mental states to others (Theory of Mind). Electroencephalographic (EEG) recordings were obtained from 20 autistic and 24 nonautistic children aged 3 to 4 years during an experimental initiating JA task. Non-autistic children showed an increase in beta band power (15-25Hz) in the right parietal electrodes, whereas autistic children did not. In both groups, beta power correlated with mentalization ability, suggesting that this neural mechanism may support mentalization during social interaction. Building on these results, we examined Theory of Mind as a more complex form of social ability. Using an experimental false belief task, EEG data were collected from 43 autistic and 58 non-autistic children aged 6 to 14 years. Preliminary results showed a significant beta-band cluster (13–23Hz) in the False Belief versus Reality condition ($p = 0.011$, cluster-corrected). A reduced beta power was observed in the non-autistic group compared to autistic children. These findings highlight the role of neural oscillations in social neurodevelopment and inform a comprehensive framework for understanding social cognition in autism.

Funding: This work was supported by the Agencia Nacional de Investigación y Desarrollo (ANID) through the FONDECYT Iniciación en Investigación program, project N°11230607.

SYMPOSIUM 2

Mechanisms of Brain Dynamics: Multiscale Computational Models and Translational Insights

Chair: Vicente Medel

Brain states in time: Distinguishing between three amplitude-defined EEG states reveals novel markers of anesthesia in neonates

Gonzalo Boncompte[1]

(1) Pontificia Universidad Católica de Chile, División de Anestesiología, Facultad de Medicina, Santiago, Chile

Adult's brain activity shows known systematic changes in response to GABAergic drugs like propofol, including modulations of electroencephalographic (EEG) alpha and delta oscillations. This is leveraged by clinical anesthesia monitors to estimate the hypnotic depth of surgical patients.

However, neonates do not showcase the same patterns of brain activity either before or during the administration of GABAergic drugs; for example, they not produce alpha oscillations. Instead, neonatal brains have been qualitatively characterized as having discontinuous (e.g., non stationary) EEG activity. Here we explored brain activity from 20 critically-ill term neonates (37-44 weeks) undergoing intensive care and requiring anesthesia for noncardiac surgery, and compared their EEG before and during a continuous rate propofol infusion. We evaluated changes in EEG activity due to propofol using two analysis strategies. First, we compared classical spectral measures averaged across time. Secondly, we segmented EEG data in time characterizing each 1s segment as isoelectric, lowvoltage, or high-voltage, based on peak amplitude. These EEG states were evaluated in terms of their occupancy, duration, number of distinct segments and internal spectral properties. We found that average spectral properties showed no significant difference due to propofol. Interestingly, neonates showed systematic increases in isoelectric EEG states occupancy, number of segments and duration. We also saw marked reductions of spectral power within low-voltage EEG states across all frequencies, but not within high-voltage states. These results introduce novel potential markers of hypnotic depth for neonates, and emphasize the usefulness of considering the dynamical and many times non-stationary nature of brain states.

Funding: Financial support and sponsorship: present work was financially supported in part by 'Concurso de Investigacion, Programa de Farmacologı´a' from the Pontificia Universidad Catolica de Chile.

Shaping Brain Rhythms: Computational Modeling of EEG Oscillations and Neurostimulation.

Mónica Otero[1]

(1) Universidad San Sebastián, Facultad de Ingeniería, Santiago de Chile, Chile

Brain rhythms are fundamental to neural communication, enabling coordination across brain regions and supporting key cognitive functions such as perception, memory, and attention. In this talk, we explore how computational modeling, grounded in brain connectivity and EEG data, can be used to understand and modulate these rhythms through neurostimulation. We will present how large-scale brain network models allow us to simulate the effects of external rhythmic stimulation at different frequencies, revealing how specific neural circuits respond depending on their intrinsic dynamics and connectivity patterns. These simulations offer insight into the frequency-specific engagement of neural populations, and how external input can shift or enhance endogenous oscillatory activity. By bridging theory, simulation, and empirical EEG data, this approach provides a framework for designing targeted and personalized neuromodulation strategies. The implications extend to both basic neuroscience and clinical applications, offering potential for improving brain health, enhancing cognitive performance, and treating neurological disorders.

Funding: Fondecyt Iniciación 11241484, Basal FB21008, Exploración 13240042

Synergistic high-order statistics in a neural network are related to task complexity and attractor characteristics.

Patricio Orio[1]

(1) Universidad de Valparaíso, Instituto de Neurociencia, Facultad de Ciencias, Gran Bretaña 1111, Valparaíso, Chile

Emergence of collective functions the brain is an open question in neuroscience, as they are believed to underlie consciousness, behavioral outputs, and brain disorders. It is unknown how measurable emergent behaviors can originate and be sustained, contributing to information processing. We studied the self-emergence of high-order interactions (HOIs) in RNNs that undergo plasticity to learn to perform cognitive tasks of different complexity. HOIs are statistical structures that are present in a group of variables but not in pair-wise interactions, and are characterized by tools from Information Theory. We trained continuous-time RNNs to perform one of the following tasks: Go/NoGo, Negative patterning, Temporal Discrimination, Contextdependent Decision making. Then, the dynamics of the hidden layer was evaluated. HOIs were characterized using the O-info and S-info metrics, at different orders of interaction taking all combinations from 3 to 11 nodes. The dimension of the trajectory was assessed by the amount of variance explained by the first 5 PCA components. In our results, training causes the dynamics of hidden layer to show HOIs with high redundancy at higher orders of interaction and synergistic interactions measured at lower order. More synergy is observed after training with the context-dependent task, while more redundancy is originated by the simpler Go/NoGo.

Synergistic interactions are correlated with more complex dynamics as suggested by a trajectory of higher dimension. Finally, we tested different pruning procedures to obtain sparser weight matrices, without observing an effect on the HOIs measured. Our results suggest that complex tasks promote the emergence of synergistic interactions.

Funding: Fondecyt grant 1241469 (ANID). Basal grant AFB240002 (ANID)

SYMPOSIUM 3

Huellas en el Camino Neurocientífico de la Dra. Katia Gysling: Su Impacto en Chile y el Mundo

Chair: Paola Haeger

Methylglyoxal-induced stress causes cellular senescence and dysregulation of ALS-associated proteins

Verónica Noches[1], Cristian Droppelmann[1], Danae Campos-Melo[1], Michael J Strong[1]

(1) Western University, Robarts Research Institute, Schulich School of Medicine & Dentistry, 1151 Richmond St, N6A 3K7, London, Ontario, Canada

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease marked by the degeneration of motor neurons, with aging being a key risk factor. Cellular senescence, a hallmark of aging, involves the cessation of cell proliferation triggered by various stressors such as DNA damage, telomere shortening, and genomic instability. This study investigates the effect of methylglyoxal (MG), a toxic metabolic byproduct, on senescence and ALS markers.

In cell lines, we demonstrate that MG increases the expression of senescence markers, including senescence-associated β-galactosidase (SA-β-gal), p16, and p53. We also observed higher levels of phosphoH2A.X, a marker of DNA damage, which was confirmed by a comet assay that revealed increased DNA strand breaks and failed DNA repair. This finding was supported by lower levels of CHD2, a chromodomain helicase DNA-binding protein involved in this process. Additionally, we found that MG triggers the expression of ALS-related markers, such as phospho-TDP-43, along with markers indicating stress granule formation. For in vivo studies, we used wild-type Drosophila melanogaster (Canton-S), adding MG to their food; we observed that MG shortens lifespan and impairs motor performance. Elevated levels of Advanced Glycation End Products, another marker of senescence, were noted after MG exposure. Lastly, we performed a Smurf assay to assess increased intestinal permeability, a reliable indicator of biological age in D. melanogaster, which showed that MG treatment resulted in positive Smurf flies. In conclusion, MG-induced stress offers a valuable model for studying aging mechanisms and their link to ALS.

Funding: This work was supported by a generous donation from the Temerty Family Foundation. M.J.S. is supported by the Canadian Institutes of Health Research (CIHR).

Mitochondrial Remodeling and Metabolic Reprogramming in Regenerative and NonRegenerative Xenopus laevis in Response to Spinal Cord Injury

Paula Slater[1]

(1) Universidad San Sebastián, Departamento de Ciencias Biológicas y Químicas, Facultad de Ciencias, Avenida del Valle Norte 725, Huechuraba, Santiago, Chile

Spinal cord injury (SCI) causes permanent motor and sensory deficits due to the limited therapies and regenerative capacity of the mammalian central nervous system. In contrast, Xenopus laevis can regenerate its spinal cord during larval (regenerative, R-stage) stages, a capacity lost after metamorphosis (non-regenerative, NRstage). This makes Xenopus a powerful model for comparing regenerative and non-regenerative responses within the same species. Mitochondria are emerging as central regulators of neuronal survival, inflammation, axon regeneration, and neural stem progenitor cell (NSPC) behavior, processes critical to SCI.

However, their temporal dynamics and metabolic adaptations during regeneration remain poorly understood. Here, we investigated these mitochondrial responses in R- and NR-stage Xenopus laevis following SCI, using electron and confocal microscopy, transgenic lines, RT-qPCR, enzymatic assays, and western blotting. In R-stage animals, SCI induced a rapid mitochondrial response in NSPCs, characterized by a reduction in mitochondrial number and an increase in swollen morphology without signs of dysfunction. This was accompanied by a shift toward aerobic glycolysis, supported by increased glycolytic transcript expression, enzymatic activity, and a transient decrease in mitochondrial membrane potential. In contrast, NR-stage animals showed a delayed mitochondrial response, mitochondrial dysfunction, and structural abnormalities. Despite this, ATP levels increased, and transcriptomic data revealed a shift toward fatty acid catabolism.

These findings suggest that efficient regeneration in Xenopus is associated with early mitochondrial remodeling and glycolytic reprogramming, whereas regenerative failure is linked to delayed, maladaptive mitochondrial responses. This work highlights mitochondrial and metabolic regulation as potential therapeutic targets for enhancing regeneration after SCI.

Funding: Funded by Fondecyt 11220624 and Centro Ciencia & Vida, FB210008 from ANID

The Lateral Septum: A key focus of Dr. Katia Gysling´s research. Its role in the regulation of feeding behavior

Ramón Sotomayor-Zárate[1], María José Covarrubias[1], Rossy Olivares-Barraza[1]

(1) Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile.

Obesity, a major global health concern, is closely linked to sedentary lifestyles and the consumption of hypercaloric, hyperpalatable diets. The neural mechanisms underlying dietinduced dysregulation of energy balance remain incompletely understood. The lateral septum (LS), a brain region involved in reward, stress, and autonomic regulation, exhibits high expression of glucagon-like peptide-1 receptors (GLP-1R), which modulate food intake. Chronic exposure to obesogenic diets (high-fat plus sucrose) induces sex-specific molecular and cellular alterations in the LS. In males, HFD increases corticotropin-releasing factor (CRF) and glial fibrillary acidic protein (GFAP) expression, indicative of neuroinflammation and stress-related responses. In females, HFD elevates dopamine D and D receptor expression, along with CRF receptor type 2 (CRF). Both sexes display increased dopamine metabolites in mesolimbic regions, suggesting altered reward processing. Additionally, HFD reduces LS GLP-1R protein levels in males, without affecting GLP-1 peptide levels. Dietary interventions restore GLP-1R expression, whereas pharmacological treatments like phentermine paradoxically increase high-fat diet intake, potentially facilitating weight regain. These findings suggest that HFD induces neuroplastic changes in the LS, disrupting homeostatic and hedonic feeding regulation via alterations in CRF, dopamine, and GLP-1R signaling pathways. The LS's involvement in neuroinflammatory and neurochemical adaptations highlights its potential as a therapeutic target for obesity and related disorders, emphasizing the importance of sex-specific approaches in addressing diet-induced neural dysregulation.

Funding: This work was supported by the National Agency of Research and Development (ANID-Chile) through FONDECYT Grant Nº124-0141 to R.S-Z. M.J.C. and R.O-B. are supported by Ph.D. fellowship from ANID N° 21210295 and N° 21200338, respectively.

YOUNG NEUROSCIENTIST SYMPOSIUM

Chair: Evelyn Avilés

Loss of Ptprd induces an increase in cortical neurons, impairing synaptic function, and contributing to autistic-like behaviors

Bastián Cortés[1], Francisca Cornejo[2], Rodrigo Meza[3], Carlos Ancatén[3], Nicolás Ardiles[3], Andrés E. Chavez[3], Pablo R. Moya[3], Gonzalo I. Cancino[1]

(1) Pontificia Universidad Católica de Chile, Faculty of Biological Sciences, Santiago, Chile
(2) Universidad Mayor, Faculty of Sciences, Santiago, Chile
(3) Universidad de Valparaíso, Faculty of Sciences, Valparaíso, Chile

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by deficits in social interaction and repetitive/stereotyped behaviors. Although the causes of ASD are still unknown, the disruption of the excitatory/inhibitory balance has been proposed as a mechanism in ASD etiology. Therefore, it is important to identify genes associated with ASD that also contribute to the maintenance of the excitatory/inhibitory balance. In this regard, the tyrosine phosphatase receptor PTPRD has been genetically linked to ASD. Moreover, Ptprd-deficient mice exhibit an increase in the number of excitatory neurons during cortical development. However, whether these deficits persist into adulthood and if the number of inhibitory neurons is also affected, remains unclear. Thus, we hypothesize that the imbalance in the number and location of excitatory and inhibitory neurons alters synaptic function in Ptprd-deficient animals, contributing to the manifestation of autistic-like behaviors.

To assess this, we performed immunofluorescence on brain sections to identify glutamatergic and inhibitory neurons in the medial prefrontal cortex (mPFC).

We complemented this with electrophysiological recordings to evaluate synaptic transmission, and behavioral assays to evaluate ASD-like behaviors in Ptprd-deficient mice
Our results showed that Ptprd-deficient mice exhibited an imbalance in the number of glutamatergic and inhibitory neurons in the mPFC. Electrophysiological recordings revealed increased excitatory and inhibitory synaptic activity in this region. Also, Ptprd-deficient mice displayed autistic-like behavior compared to wild-type littermates.

These findings suggest that the imbalance of glutamatergic and inhibitory neurons in the mPFC disrupts synaptic function, potentially contributing to the emergence of autistic-like behaviors in Ptprd-deficient animals.

Funding: Postdoctoral UC Fellowship

Neurochemical analysis of social buffering of conditioned fear responses in rats.

Takumi Yamasaki[1,2], Yasushi Kiyokawa[1], Arisa Munetomo[1], Yukari Takeuchi[1]

(1) Laboratory of Veterinary Ethology, the University of Tokyo, Graduate School of Agricultural and Life Sciences, Department of Animal Resource Sciences, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, Japan
(2) Japan Society for the Promotion of Science, Research fellow

A growing body of evidence indicates that social interaction is crucial for better health and well-being in animals. One such example is social buffering, the phenomenon in which stress responses are mitigated by affiliative social partners. In rats, even unfamiliar conspecifics can mitigate conditioned fear responses. Here, we investigate the neural mechanisms underlying this phenomenon. We first found that intraperitoneal administration of an opioid receptor antagonist naloxone increased freezing despite the presence of an unfamiliar rat, suggesting that opioid receptors play a role in social buffering.

Because this blockade was accompanied by reduced Fos expression in the nucleus accumbens (NAc), we next administered naloxone locally to the NAc. As a result, microinjection into the dorsal part of the anterior NAc (adNAc), but not into the ventral or posterior subregions, blocked social buffering. These effects were primarily mediated by kappa-opioid receptors because microinjection of a kappa-opioid receptor antagonist norBNI blocked social buffering, while microinjection of a kappa-opioid receptor agonist U50,488 induced it. Retrograde tracing revealed preferential projections to the adNAc from the Anteromedial thalamic nucleus (AM), Interanteromedial thalamic nucleus (IAM), and Rhomboid nucleus (Rh). Subsequent Fos analysis combined with retrograde tracing indicated that projections from AM and IAM, but not Rh, were activated during social buffering.

These findings illustrate a kappa-opioid receptor-mediated neural circuit underlying social buffering of conditioned fear responses in rats. Financing: This study was supported by JSPS KAKENHI grant numbers JP24H00538, JP25KJ0757, JP25K21742, and JSPS Bilateral Program Number JPJSBP120259911.

Unraveling cortical synaptic dysfunction and altered synaptic pathways in Parkinson's disease

Dayana Perez Acuna[1,4], Saroj Sah[1,4], Thomas Goralski[2,4], Michael X. Henderson[2,4], Thomas Biederer[1,3,4]

(1) Yale University, Department of Neurology, School of Medicine, 100 College, New Haven, CT, USA
(2) Van Andel Institute, Department of Neurodegenerative Science, Grand Rapids, MI, USA
(3) Yale University, Department of Neuroscience, School of Medicine, New Haven, CT, USA
(4) Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, Chevy Chase, MD, USA

Brain connectivity is severely disrupted in neurodegenerative disorders, but the underlying pathways of cellular dysfunction remain to be defined. The presence of protein inclusions in the brain is a hallmark of neurodegenerative diseases. In Parkinson's disease (PD), the presynaptic protein a-synuclein (α-syn) aggregates within neuronal cell bodies and neurites. These aggregates originate in discrete regions of the brain, spreading to other regions as the disease progresses. The cellular consequences of its aggregation at the synapse are poorly understood, but cortical a-synuclein pathology correlates with cognitive decline in PD.

Notably, intratelencephalic (IT) neurons in cortical layers 5 and 6 exhibit increased susceptibility to α-syn accumulation. To investigate synaptic alterations, we characterize synaptic transmission in cortical layer 5 neurons in the preformed α-syn fibril (PFF) mouse model of PD. We observed reduced excitatory synaptic function, synapse density, and dendritic spine abnormalities, confirmed using high-resolution imaging, supporting vulnerability and progressive loss of excitatory synapses.

To gain molecular insight into dysregulated synaptic pathways, we performed gene ontology analyses of whole-transcriptome signatures from neurons bearing α-syn pathology and identified conserved gene expression changes in pathways involved in synaptic vesicle cycle, postsynapse density, and synapse organization. In parallel, we identified upregulated genes associated with resilience, suggesting the presence of endogenous mechanisms that may counteract synaptic decline. Single-cell RNAseq data confirm our findings. Together, these results provide insight into how synaptic structure and function are affected in PD and can identify candidate targets involved in early synapse loss, guiding future therapeutic strategies.

Funding: This study is funded by the Aligning Science Across Parkinson's (ASAP) grant ASAP-020616.

G Protein-Coupled Receptor Kinases as a novel target for drug addiction vulnerability

Rafael Gatica[1], Bastian Ignacio Rivera[1], Simón Dávila[1], Carolina Pino[1], Catalina Starocelsky[1], Fernando González-Reinoso[1], Robinson Moreno-Martínez[2], Pilar Aguilera-Maturana[1], Benjamin Manríquez[1], Mariana Garcia[1], Francisca Codocedo[1], Cristobal Guzmán[1], Martina Schenke[1], Angélica del Pilar Escobar[2], María Estela Andrés[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Av. Libertador Bernardo O'Higgins 340, Santiago, Chile
(2) Universidad de Valparaíso, Instituto de Fisiología, Facultad de Ciencias, Av. Gran Bretaña 1111, Valparaíso, Chile

While prolonged drug consumption can lead to addiction, only a subset of individuals develops compulsive use. High novelty-seeking (NS) is a crucial endophenotype linked to increased drug addiction vulnerability, characterized by a hyperdopaminergic profile and reduced dopamine D2 receptor (D2R) expression in the striatum. However, the underlying mechanisms for this association are unclear. G protein-coupled receptor kinases (GRKs) modulate desensitization, internalization, and recycling of receptors like D2R. Although GRKs regulate the dopaminergic system and drug-induced locomotor effects, their role in NS behavior has not been explored. Our study investigated GRK relevance in D2R regulation and NS behavior in rodents. Using immunofluorescence, we analyzed the presynaptic and postsynaptic localization of GRKs in mesencephalic dopaminergic circuits of adult male Sprague Dawley rats and C57BL/6J mice. We found GRK2 and GRK5 expressed in medium spiny neurons (MSNs) and dopaminergic neurons, while GRK3 and GRK6 showed more restricted expression. Using western blot, we found that acute injection of the D2R agonist quinpirole (QNP) transiently increased GRK2 levels in the nucleus accumbens, with GRK6 levels increasing 24 hours post-injection in rats, but not in mice. Furthermore, quantifying GRK levels in striatal synaptosomes from high responder (HR) and low responder (LR) rats to novelty revealed that HR rats exhibited lower dorsal striatum GRK2 and higher GRK5 levels. Finally, pharmacological inhibition of GRK2/3 reduced locomotion in a novel context in HR rats. Our findings suggest that D2R stimulation modulates striatal GRKs, and GRK activity influences novelty-seeking behavior, implying a significant role in drug addiction vulnerability.

Funding: Fondecyt Postdoctorado 3230573 to RIG, Doctorado Nacional 21221349 (ANID) Fellowship to BIR, Puente UC to MEA, FONDECYT Iniciacion 11240331, CENFI DIUV-CI-01/2024, Núcleo milenio EpiNeuro, NCN 2023-032 to AE.

SYMPOSIUM 4

Decoding Fear Memories Outside the Box

Chair: Alexies Dagnino

Sex-specific effects of developmental alcohol exposure: Delayed fear extinction and increased alcohol intake in female rats

Paola Andrea Haeger Soto[1,2], Camila Morales[1,2], Sebastián Estay[1], Montserrat Olivares-Costa[1]

(1) Universidad Católica del Norte, Departamento Ciencias Biomédicas, Facultad de Medicina, Larrondo 1281, Coquimbo, Chile
(2) Millennium Nucleus of Neuroepigenetics and Plasticity (EpiNeuro), Santiago, Chile

Prenatal and early postnatal ethanol exposure disrupts normal brain development, particularly in regions involved in memory, emotional regulation, and reward processing. These alterations can result in long-lasting behavioral consequences.
We previously showed that female—but not male—rats exposed to ethanol from gestational day 0 to postnatal day 7 exhibited impaired extinction of aversive memories formed through auditory fear conditioning (AFC). These females also consumed more ethanol and had lower levels of DOPAC in the nucleus accumbens, suggesting a sex-dependent susceptibility to persistent fear memories and increased alcohol intake.

To better understand the neural mechanisms involved, we examined the medial prefrontal cortex (mPFC), a brain region critical for extinction memory and reward regulation. In ethanol-exposed females—but not in males—we observed increased inhibitory synaptic transmission in layers II/III of the mPFC, without changes in excitatory (glutamatergic) transmission compared to controls.

Together, these findings reveal sex-specific alterations in prefrontal cortical circuits that may underlie the difficulty in regulating fear responses observed in ethanol-exposed females. This research underscores the importance of considering sex differences when studying the long-term impact of early alcohol exposure on emotional regulation, memory, and vulnerability to psychiatric and substance use disorders.

Funding:
PEW innovation fund, ANID-MILENIO (NCN2023_32)

Contribution of neuropeptide S (NPS) to cued fear extinction and stress response in virgin and lactating females

Marianella Masis-Calvo[1], Inga D. Neumann[2]

(1) Universidad de Costa Rica, Centro de Investigación en Neurociencias, Facutad de Ciencias, Montes de Oca, San Jose, Costa Rica
(2) University of Regensburg, Department of Behavioral and Molecular Neurobiology, Faculty of Biology and Preclinical Medicine, Universitätsstraße 31, Regensburg, Germany

The Neuropeptide S (NPS) system is a conserved neuromodulatory pathway implicated in arousal, emotional, and stress regulation. Although well-characterized in males, its function in females—particularly across reproductive states such as the estrous cycle and lactation—remains understudied. NPS is synthesized in discrete brain regions, including the locus coeruleus, hypothalamus, and amygdala, while its receptor (NPSR) is broadly expressed in limbic, cortical, and peripheral tissues. Centrally, NPS activates the hypothalamic-pituitary-adrenal (HPA) axis and facilitates fear extinction in males.

We first examined the NPS system under basal conditions in lactating and virgin female rats. Lactating females showed increased NPS—but not NPSR—mRNA expression in stress-related brain regions. In a following cued fear conditioning experiment, virgin females were classified by estrous phase (high vs. low estradiol). All groups acquired fear similarly. Before extinction, animals received intracerebroventricular NPS or antagonist infusions. NPS facilitated extinction only in low-estradiol virgins and lactating females. To evaluate peripheral effects (5 days later), the same infusions were followed by plasma measurements of corticosterone, oxytocin, and NPS. NPS increased corticosterone only in virgins and elevated oxytocin in both groups, without altering plasma NPS levels. Finally, NPS protein levels were quantified in cerebrospinal fluid (CSF), plasma, and mammary glands under control and stress conditions. CSF-NPS increased post-stress regardless of reproductive state. Plasma NPS were higher in lactating females across conditions. In mammary tissue, both stress and reproductive status significantly modulated NPS. These findings highlight dynamic, hormone-dependent regulation of the NPS system, with relevance to stress adaptation, fear extinction.

Funding: This work was supported by Universidad de Costa Rica under the Grant ALECOSTA-57176158 (M.M.), and by Deutsche Forschungsgemeinschaft (GRK2174, Ne465/36.1 to I.D.N.).

Social Fear Memory: A Framework for Understanding Social Stress and Psychopathology.

Alexies Dagnino[1,2], Ann Mary Iturra-Mena[3]

(1) Universidad de Valparaíso, Institute of Physiology, Faculty of Sciences, Gran Bretaña 1111, Playa Ancha, Valparaíso, Chile
(2) Millennium Institute for Depression and Personality Research (MIDAP), Santiago, Chile
(3) Columbia University, Department of Psychiatry, DATA SCIENCE INSTITUTE, 1051 Riverside Dr, New York, USA

While social defeat is stressful for rodents and humans; under some conditions, it can lead to persistent social avoidance. Our study proposes that the experience of social defeat promotes the

consolidation of social fear memory via associative learning mechanisms, paralleling classical fear conditioning. We examine how the context of defeat becomes a conditioned stimulus, while the aggressor serves as the unconditioned stimulus, producing fear-related behaviors such as freezing. The consolidation and expression of social fear memory rely on distributed neural circuits that integrate threat appraisal, contextual cues, and social information. These include canonical fear-processing hubs, the amygdala, and prefrontal cortex, as well as regions specialized for social behavior such as the nucleus accumbens. Neuroendocrine systems including stress hormones, norepinephrine, oxytocin, and vasopressin modulate these pathways in context-dependent ways, allowing either social vigilance or buffering. Understanding social defeat as a form of fear memory highlights targets for intervention across acquisition to extinction phases. This framework provides a foundation for refining pharmacological and psychological treatments for stress-related disorders rooted in social trauma.

Funding: This study was funded by CIESAL Grant Number CIDI08/2017 and ANID – Millennium Science Initiative Program / Millennium Institute for Research on Depression and Personality – MIDA

Social buffering of conditioned fear responses in rats

Yasushi Kiyokawa[1]

(1) Laboratory of Veterinary Ethology, The University of Tokyo, Tokyo, Japan

In gregarious species, social behavior is one of the indispensable aspects of their lives. Therefore, it is not surprising that social variables influence neural, endocrine, and immune outcomes. One example is social buffering, the phenomenon in which the presence of affiliative conspecifics mitigates stress responses. We conducted a series of studies in rats to examine social buffering using auditory fear conditioning. When the fear-conditioned subjects were exposed to the conditioned stimulus (CS) alone, conditioned fear responses, including freezing, were observed. However, the presence of an unfamiliar same-sex rat (associate) completely blocked these responses, suggesting that social buffering ameliorates conditioned fear responses. Subsequent analyses revealed that the olfactory signal alone was necessary and sufficient for inducing social buffering. Parallel investigation of the characteristics of social buffering revealed that not all rats provided buffering effects to the Wistar subjects. Specifically, Wistar rats and the descendants of Wistar rats acted as social buffers, whereas rats established independently from Wistar rats were found to be non-buffers. Based on these findings, we searched for the chemicals responsible for social buffering within the body odor of the social buffers. We found that 2-methylbutyric acid alone was sufficient to induce social buffering. Therefore, we refer to it as an appeasing pheromone. We believe that a deeper understanding of social buffering could significantly advance our knowledge of sociality in animals, while also paving the way for novel approaches to fear regulation.

Funding: This study was supported by JSPS KAKENHI grant numbers JP24H00538 and JP25K21742, and JSPS Bilateral Program Number JPJSBP120259911.

SYMPOSIUM 5

Fueling the Mind: The Role of Energy Metabolism in Neural Learning and Behavior

Chair: Pedro Maldonado

The Energy Homeostasis Principle, how behavior would emerge from metabolic constraints

Rodrigo Vergara[1,6], Alejandro Luarte[5], Cristobal Moenne[4], Ismael Jaras[3], Marcos Orchard[3], Pedro Maldonado[2,6]

(1) Universidad Metropolitana de Ciencias de la Educación, Kinesiología, Facultad de Artes y Educación Física, Dr. Luis Bisquert 2765, Ñuñoa, Región Metropolitana, Santiago, Chile
(2) Universidad de Chile, Neurociencias, Facultad de Medicina, Independencia 1027, Independencia, Santiago, Chile
(3) Universidad de Chile, Ingeniería Electrica, Facultad de Ciencias Físicas y Matemáticas, Av. Beauchef 850, Santiago, Santiago, Chile
(4) Pontificia Universidad Católica de Chile, Kinesiología, Facultad de Medicina, Av. Vicuña Mackenna 4860, Macul, Santiago, Chile
(5) Universidad de los Andes, Medicina, Facultad de Medicina, San Carlos de Apoquindo 2300, Las Condes, Santiago, Chile
(6) Centro Nacional De Inteligencia Artificial, NA, NA, Av. Vicuña Mackenna 4860, Macul, Santiago, Chile

Current efforts to explain the emergence of behavior and understanding from neural mechanisms often employ a top-down approach, such as the Free Energy Principle (FEP), which maps mental states to neuronal substrates. However, these approaches frequently overlook the fundamental biophysical constraints governing neural tissue. We will introduce the Energy Homeostasis Principle (EHP), a complementary and distinct bottom-up framework that proposes energy balance—between income, expenditure, and availability—as the primary determinant of neuronal dynamics, from the molecular to the behavioral level.
Neurons are characterized by their exceptionally high energy consumption and strict aerobic metabolism, making them acutely sensitive to energy limitations. The largest energy expenditures in neurons are associated with action potentials and post-synaptic potentials, allowing for a reinterpretation of plasticity within an energy context. Through their synapses, neurons impose energy demands on post-synaptic neurons, forming a closed-loop system that modulates local circuit dynamics and, ultimately, impacts functional neural networks.

This framework proposes that the emergence of behavior can be explained through these localized energy requirements, as evidenced in silico. While acknowledging that EHP, in its current form, is a foundational step, it establishes a testable, neuron-centric framework with the potential to explain the complex emergence of understanding.

Funding: FONDECYT de Exploración 13240026

Morphological and functional changes induced by glucose levels in cortical neurons in primary culture

Jimena Sierralta[1], Estefania López[1], Alejandro Luarte[2]

(1) Universidad de Chile, Neurociencia, Medicina, Independencia 1027, Santiago, Chile

(2) Universidad de los Andes, Centro de Investigación e Innovación Biomédica, Medicina, Av. Mons. Álvaro del Portillo 12.455, Las Condes, Santiago, Chile

In this work, we explore, in cortical primary cultures, the Energy Homeostasis Principle (EHP), where the balance between energy intake, expenditure, and availability is a critical parameter determining neural circuit formation and dynamics. The EHP implies that regulatory mechanisms responsible for synaptic plasticity changes reflect the requirement of available energy resources for neuronal function. Therefore, exposing cultures to constraints in the availability of glucose may trigger changes in the number, morphology, and efficiency of the synapses formed in the culture, where lower availability (over a minimum) should produce less and more efficient connectivity. Normal glucose concentration in neuronal primary cultures is 25 mM, while plasma glucose is 5 mM. In addition, many of the experimental conditions deplete the culture of glial cells. We will show the changes induced in the morphology and synaptic abundance in cultures grown in the presence of glial cells and with less than half the amount of glucose.

Funding: This research is supported by the Project Exploración 13240026

Scale-spanning cross-talk between metabolism and information processing

Luis Felipe Barros Olmedo[1,2], Ignacio Fernández-Moncada[3], Giovanni Marsicao[3], Iván Ruminot[1,2], Aiman Saab[4], Bruno Weber[4]

(1) Centro de Estudios Científicos CECs, Biology, Arturo Prat 514, Valdivia, Chile
(2) Universidad San Sebastián, Valdivia, Chile.
(3) University of Bordeaux, Bordeaux, France.
(4) University of Zurich, Institute of Pharmacology and Toxicology, Switzerland.

The research fields of brain intercellular signaling and brain energy metabolism evolved separately. One dealt with neurotransmitters and their receptors, mediating fast communication between distant neurons and the assembly of vast neural networks underlying diverse brain functions. The other focused on enzymes and transporters, tissue compartmentation, and the exchange of substrates and products between neighboring neurons and glial cells. High-order brain functions like cognition operate over long distances and can be fast. In contrast, metabolism is slow and, being limited by diffusion, operates over short distances. However, this comfortable division is now being challenged by the realization that lactate, beta-hydroxybutyrate, ATP/adenosine and other key elements of the universal metabolic core also play the role of intercellular signals in brain tissue, acting via G protein-coupled receptors and other targets. Here we discuss the possible physiological meaning of such promiscuity. By arguing that it is no longer possible to understand signaling without understanding metabolism, and vice versa, our purpose is to raise awareness of the ongoing convergence and foster interdisciplinary collaboration. Meanwhile, new technical developments are making the interphase between the two fields more amenable to the non-initiated.

Funding: This work was funded partly by ANID-Fondecyt projects 1230145 (L.F.B.) and 1230682 (I.R.).

Computational Insights on Energy-Dependent Learning in Small Neural Networks

Christ Devia[1,2], Matías Francisco Urrea Cabezas[1,2], Samuel Madariaga[1,2], Mircea Petrache[1,3,4], Pedro Maldonado[1,2]

(1) National Centre for Artificial Intelligence, Vicuña Mackenna 4860, Macul, Santiago, Chile.
(2) Universidad de Chile, Departamento de Neurociencia, Facultad de Medicina, Av. Independencia 1027, Santiago, Chile
(3) Pontificia Universidad Católica de Chile, Departamento de Matemáticas, Facultad de Matemáticas, Av Vicuña Mackenna 4860, Santiago, Chile
(4) Instituto de Ingenieria Matemática y Computacional, Av Vicuña Mackenna 4860, Santiago, Chile

One of the key mechanisms of learning in neural circuits occurs through modifications in the connectivity between neurons. Like any cellular process, learning must be supported by an adequate energy budget. Currently, the role of energy in learning processes is an area of active research in neuroscience. Of particular interest is the area that relatesenergy availability and consumption to plastic processes, where learning is driven by the need to maintain energy within neuron's budget. From this perspective, learning processes could be interpreted as adaptations that minimize the large and inefficient energy excursions that occur in relation to novel external stimuli. On the other hand, currently, thecomputational models underlying major advances in artificial intelligence (AI) are based on the assumption that learning occurs by minimizing the prediction error made by the model for a given input. Specifically, in this context, learning occurs as a modification of the connectivity between these artificial neurons, and these modifications are being guided by a mathematical optimization process. However, until now, the role of neuron energy constraints on learning has not been carefully considered in artificial neural networks. Here, we compare biological and artificial learning processes, and, by studying a small artificial neural network that incorporates energy-dependent parameters, we provide someinsights into how energy constraints shape network dynamics and function.

Funding: National Center for Artificial Intelligence CENIA, Chile FB210017, Basal ANID, Chile.ANID Proyectos de Exploración 13240026

ORAL COMMUNICATIONS I

Chairs: Angelina Palacios and Rodolfo Madrid

Umbilical cord mesenchymal stem cell-derived extracellular vesicles are selectively protective in the Pentylenetetrazole model of epileptogenesis.

Maxs Mendez-Ruette[1,2], Katherine Corvalán[1], Daniela Corvalán-Bustos[1], Ariel Caviedes[1], Pablo Lazcano[1,2], Aliosha Figueroa[2,3], Gino Nardocci[1,2,4], Francisca Alcayaga[2,3], Federico Batiz[1,4], Alejandro Luarte[1,2,4], Úrsula Wyneken[1,2,4]

(1) Universidad de los Andes, Centro de Investigación e Innovación Biomédica (CiiB), San Carlos de Apoquindo 2500, Santiago, Chile
(2) Center of Interventional Medicine for Precision and Advanced Cellular Therapy (IMPACT), San Carlos de Apoquindo 2500, Santiago, Chile
(3) Cells for Cells, San Carlos de Apoquindo 2500, Santiago, Chile
(4) Universidad de los Andes, Escuela de Medicina, Facultad de Medicina, Monseñor Álvaro del Portillo 12455, Santiago, Chile

Temporal lobe epilepsy affects over 50 million people worldwide, and approximately one-third of patients remain resistant to current antiepileptic drugs, highlighting the need for novel therapeutic strategies. Emerging evidence points to neuroinflammation and excitotoxicity as key contributors to epileptogenesis. Mesenchymal stem cell (MSC)-derived extracellular vesicles (EVs) offer a promising, cell-free therapeutic alternative due to their immunomodulatory properties. In this study, we evaluated the effects of EVs derived from two MSC sources: human umbilical cord (UC-EVs) and menstrual fluid (Mens-EVs) in the pentylenetetrazole (PTZ)-induced rat model of epilepsy. Systemic administration of UC-EVs 24 hours prior to PTZ injection abolished seizure-induced mortality and decreased seizure duration and intensity. Histological and molecular analyses revealed that UC-EVs attenuated neuronal apoptosis and preserved neuronal density, when evaluated in the primary somatosensory cortex and hippocampal CA1 region. Furthermore, UC-EVs restored PTZ-induced microglial morphological changes in the dentate gyrus, without affecting astrocyte reactivity or morphology. Conversely, Mens-EVs failed to reduce seizure severity and even exacerbated excitotoxicity markers after PTZ, potentially by enhancing neuronal excitability. Transcriptomic analysis of these vesicles revealed that UC-EVs are enriched in microRNAs predicted to target and suppress multiple pro-inflammatory signaling pathways, supporting their observed immunomodulatory effects. These findings suggest that UC-EVs confer significant neuroprotection by mitigating excitotoxic damage and microglial activation during temporal lobe epileptogenesis. Our results support the therapeutic potential of UC-EVs as a non-invasive intervention during epileptogenesis and underscores the importance of the EV source and their miRNA cargo in determining efficacy and safety.

Funding: Regular Fondecyt 12000693&1240604 (to UW) and IMPACT, #FB210024

Ketogenic diet administration later in life improves memory by modifying the synaptic cortical proteome via the PKA signaling pathway in aging mice

Diego Acuña-Catalán[1], Samah Shah[2], Cameron Wehrfritz[2], Mitsunori Nomura[2], Alejandro Acevedo[3], Cristina Olmos[1], Gabriel Quiroz[1], Hernán Huerta[6], Joanna Bons[2], Estibaliz Ampuero[7], Ursula Wyneken[8], Magdalena Sanhueza[4], Felipe Arancibia[4], Darwin Contreras[9], Julio César Cárdenas[1,2,6,10], Bernardo Morales[9], Birgit Schilling[2], John C. Newman[2], Christian González-Billault[1,2,3,4,5]

(1) Center for Geroscience, Brain Health, and Metabolism (GERO). Universidad de Chile, Department of Biology, Faculty of sciences, Las Palmeras 3425, Santiago, Chile
(2) The Buck Institute for Research on Aging, Redwood Blvd 94945, Novato, CA, United States of America
(3) Institute of Nutrition and Food Technology (INTA). Universidad de Chile, El Líbano 5524, Santiago, Chile
(4) Universidad de Chile, Department of Biology, Sciences, Las Palmeras 3425, Santiago, Chile
(5) Universidad de Chile, Department of Neurosciences, Faculty of Medicine, Avenida Independencia 1027, Santiago, Chile
(6) Center for Integrative Biology. Universidad Mayor, Faculty of Sciences, Camino la Pirámide 5750, Santiago, Chile
(7) Neurobiology of Behavior Laboratory. Universidad de Santiago de Chile, Department of Biology, Av. Alameda Libertador Bernardo O'Higgins, 9170022, Santiago, Chile
(8) IMPACT, Center for Interventional Medicine for Precision and Advanced Cellular Therapy. Universidad de Los Andes, Faculty of Medicine, Santiago, Chile
(9) Laboratory of Neuroscience. Universidad de Santiago de Chile, Faculty of Chemistry, Av. Alameda Libertador Bernardo O'Higgins, 9170022, Santiago, Chile
(10) Department of Chemistry and Biochemistry and Center for Aging and Longevity Studies. University of California, 1210 Cheadle Hall, Santa Barbara, CA, United States of America

Aging compromises brain function, leading to cognitive decline. Dietary interventions such as the cyclic ketogenic diet (KD) improve memory in aged mice after long-term administration, yet their short-term effects later in life and the molecular mechanisms that govern such changes remain unclear. Here, we explore the impact of a short-term KD treatment starting at the elderly stage on the brain function of aged mice. Behavioral testing and long-term potentiation (LTP) recordings reveal that KD improves working memory and hippocampal LTP. Furthermore, the synaptic proteome of aged mice fed KD long-term shows evidence of changes predominantly at the presynaptic compartment associated with the protein kinase A (PKA) signaling pathway. These findings were corroborated in vivo by western blot analysis, revealing high BDNF abundance and PKA substrate phosphorylation, which correlates with cognitive improvements. Overall, we show that a KD modifies brain function even when it is administered later in life and recapitulates molecular features of long-term administration, including the PKA signaling pathway, thus promoting synaptic plasticity at advanced age.

Funding: Fondecyt Grant #1180419, ANID Scholarship #75200183 FONDAP/15150012 IMPACT #FB210024 Fondecyt Grant #3190897 NIH Grant AG06733 NIH Grant 1S10 OD016281-01 to JCN.

Unveiling the Role of Transglutaminases in Brain Development, Transcriptomics and Function: The Case of Dopaminergic Neurons

Isidora Almonacid-Torres[1], Joaquín Almonacid Torres[1], Paulina Gómez[1], María Contanza González-Ramírez[1], Rafaella V Zárate[2], María Estela Andrés[1], Carlos Oliva[1], Jorge M Campusano[1]

(1) Pontificia Universidad Católica de Chile, Ciencias Biológicas, Santiago, Chile
(2) Universidad de Antofagasta, Instituto Antofagasta, Antofagasta, Chile

Transglutaminases (TGs) are a family of enzymes characterized by their calcium-dependent transamidation activity. In higher mammals, out of the 8 catalytically active TG, TG2 is the member with the highest expression in the brain. Intriguingly, TG2 KO mice show no major neurodevelopmental abnormalities. This might be explained by compensation by the other 5 TG members also expressed in mammalian CNS. Thus, simpler animal models are needed to study the contribution of TGs to brain formation and operation. Drosophila melanogaster has only one TG-encoding gene (dTg), but little is known of the roles of this protein in fly brain development or physiology.
In this study, we observed that fly mutans for dTg showed marked morphological alterations in the fly mushroom body and a notable reduction of brain dopaminergic neurons. Cultured dopaminergic neurons from dTg knock-down larval brains exhibited reduced neurite branching when compared to control, supporting a contribution of dTG to the development of dopaminergic neurons. Furthermore, dTG-deficient animals presented decreased locomotion and strong asocial-like phenotype, two behaviors associated to the dopaminergic system. Interestingly, expressing human TG6 under the control of the fly endogenous dTg promoter in the mutant background rescued the social behavior while failing to restore motor output. Transcriptomics experiments revealed changes in the expression of several genes associated with neurogenesis and neurodevelopment in the brains of dTG-deficient animals compared to controls, which are correlated to changes in histone dopaminylation. These gene expression alterations are partially rescued in dTG mutant animals expressing hTG6.

Funding: Funded by FONDECYT Grants 1231556 (Jorge Campusano) and 1231685 (Carlos Oliva). Supported by ANID doctoral fellowship N° 21240414.

Periodontitis-induced immune imbalance triggers CD4+ T cell-mediated neuroinflammation via a periphery-to-brain axis

Carolina Rojas[1,2], Pablo Lazcano[1,3], Jorge Concha[1], Gonzalo Parra[2], Benjamín Mora[2], Maxs Méndez-Ruette[1,3], María Luisa Mizgier[1,4], María José Bendek[1,4], Katina Schinnerling[5], Pablo Berríos-Cárcamo[6], Úrsula Wyneken[1,3], Alejandro Luarte[1], Alejandra Chaparro[1,4]

(1) Universidad de Los Andes, Centre for Biomedical Research and Innovation (CiiB), Faculty of Medicine, Av. Monseñor Álvaro del Portillo 12455, Santiago, Chile.
(2) Universidad de Los Andes, Department of Growth Development and Public Health, Faculty of Dentistry, Av. Monseñor Álvaro del Portillo 12455, Santiago, Chile.
(3) Universidad de Los Andes, IMPACT, Center of Interventional Medicine for Precision and Advanced Cellular Therapy, Av. Monseñor Álvaro del Portillo 12455, Santiago, Chile.
(4) Universidad de Los Andes, Oral Pathology and Conservative Dentistry Department, Faculty of Dentistry, Av. Monseñor Álvaro del Portillo 12455, Santiago, Chile.
(5) Universidad Andrés Bello, Biologic Sciences Department, Life Sciences Faculty, República 440, Santiago, Chile.
(6) Clínica Alemana-Universidad del Desarrollo, Regenerative Medicine Centre, Faculty of Medicine, Av. Las Condes 12461, Santiago, Chile.

Pathological neuroinflammation is a central contributor to neurodegeneration, orchestrated by complex interactions between brain-resident microglia and infiltrating or circulating leukocytes. Peripheral inflammation can disrupt central nervous system (CNS) immune homeostasis, with T cells playing dual roles: effector T cells driving damage, and regulatory T cells (Tregs) conferring neuroprotection. Periodontitis, a chronic immune-inflammatory gum disease triggered by dysbiosis, has been increasingly associated with neurodegeneration, yet the underlying neuro-immune mechanisms remain elusive. Here, we investigated the effects of periodontitis on peripheral and brain immunity, focusing on the cervical lymph nodes (cLNs)/ blood-brain axis and microglia-T cells interactions. Furthermore, we examined whether periodontal extracellular vesicles from Porphyromonas gingivalis (Pg-OMVs) or periodontitis patients (hEVs) can act as neuroinflammatory response drivers.

Ligature-induced periodontitis, but not Pg-OMVs alone, disrupted peripheral immune homeostasis, increasing $CD4^+$ conventional T cell (Tconv) accumulation and elevating the convT/Treg ratio in cLNs and blood. In the brain, neuroinflammation was evidenced by MHC-II upregulation on both resting and activated microglia. Notably, despite peripheral Treg reduction, their frequency in the brain was significantly elevated, suggesting an endogenous compensatory neuroprotective response. In vitro, both Pg and hEVs activated NF-κB and IRF inflammatory pathways, promoted CD11b phagocytic marker upregulation on human monocytes and microglial polarization towards a proinflammatory reactive phenotype. Thus, while periodontal EVs possess neuroinflammatory potential, CNS inflammation in vivo requires full disease context.

These results identify a novel neuro-immune axis wherein periodontitis drives T cell–microglia-mediated neuroinflammation, underscoring the relevance of oral health as a key modulator of CNS immunity and neurodegeneration risk.

Funding: Fondecyt Postdoctorado 3240581 (CRP), Fondecyt Inicio 11230418 (MLM), Fondecyt Inicio 11220601 (AL), Fondecyt Regular 1211471 (ACh) and 1240604 (UW), ANID CHILE.

Targeting necroptosis to halt neural retina degeneration in the hOPA1delTTAG mouse model of Dominant Optic Atrophy

Macarena S Arrázola[1], Concepción Panadero-Medianero[1], Alexandra Iribarren[1]

(1) Universidad Mayor, Center for Integrative Biology, Faculty of Sciences, Camino la Pirámide 5750, Santiago, Chile

Dominant Optic Atrophy (DOA) is a hereditary optic neuropathy caused by mutations within OPA1 gene. Degeneration of retinal ganglion cells (RGC) and optic nerve (ON) leads to progressive blindness in DOA, although the underlying mechanism remains unknown. We previously identified necroptosis as a key regulator of axonal degeneration. Upon activation, the necrosome complex (RIPK1-RIPK3-MLKL) assembles, triggering membrane permeabilization and disrupting organelles such as mitochondria. The mitochondrial phosphatase phosphoglycerate mutase 5 (PGAM5) interacts with RIPK3, recruiting the necrosome to mitochondria and promoting mitochondrial fragmentation via Drp1 dephosphorylation. Whether necroptosis contributes to DOA pathophysiology by promoting optic nerve atrophy and loss of vision has not been previously explored.
Usingex vivo and in vivo approaches, we evaluated necroptosis activation in the retina and ON of hOPA1delTTAG mice. Accumulation and interaction of phosphorylated-RIPK3 and PGAM5 were detected in OPA+/- retina and in axonal projections of retina explants. Neuronal RIPK3 knockdown, achieved via intravitreal delivery of an AAV-PHP.be-shRipk3 vector in OPA1+/- mice- effectively delayed axonal degeneration in the ON, prevented RGC loss, and improved visual function assessed by the mice optomotor response. Pharmacologic inhibition of RIPK3 or PGAM5 similarly prevented retinal degeneration in OPA1+/- mice. Our preclinical study reveals necroptosis as a druggable target for treating optic neuropathies such as DOA, with potential relevance for other retinal diseases characterized by early and prominent optic atrophy.

Funding: Fondecyt 11220120

Modulation of Neurodevelopmental Phenotypes by Fatty Acid Supplementation in a Drosophila Model of Autism Spectrum Disorder

Javiera Allup-Gonzalez[1], Luis Torres-Gomez[1], Sofía Paredes-González[1], Esteban Contreras Sepúlveda[1]

(1) Laboratory of Drosophila's Neurogenetics, Departament of Cell Biology, Faculty of Biological Sciences, University of Concepcion, Concepcion, Chile

Autism Spectrum Disorder (ASD) is a multifactorial neurodevelopmental condition characterized by persistent impairments in social communication, repetitive behaviors, and neurological comorbidities. Among environmental factors, nutrition—particularly polyunsaturated fatty acids (PUFAs)—has gained attention for its critical role during brain development. Here, we explored the effects of cod liver oil supplementation using a Drosophila melanogaster model with neuronal knockdown of Neurexin-1 (Nrx-1), the fly ortholog of human NRXN1, a gene strongly linked to ASD. Neurexins are presynaptic cell adhesion molecules crucial for synaptic function and plasticity, with mutations frequently associated with neurodevelopmental disorders.

Flies with neuronal Nrx-1 knockdown (elav-GAL4>UAS-Nrx1-RNAi) and controls (elav-GAL4>UAS-GFP-RNAi) were used to characterize ASD-relevant phenotypes: (i) mechanical-induced seizures, (ii) courtship behavior, (iii) sleep patterns and (iv) presynaptic density by immunofluorescence of the marker Bruchpilot (Brp). Controls provided baseline phenotype comparison. For nutritional intervention, Nrx-1 knockdown flies were divided into two groups: standard media versus media supplemented with 3% v/v cod liver oil (PUFA-rich source).

Nrx-1 knockdown increased seizure severity, prolonged mating latency, elevated total sleep time, and reduced Brp density. PUFA supplementation partially rescued the phenotype: it reduced courtship latency, restored daytime sleep duration, and rescued Brp synaptic levels. However, seizure susceptibility remained unaffected.

These findings suggest that our Drosophila model successfully reproduces core ASD-like features associated with Nrx-1 downregulation. Cod liver oil supplementation partially ameliorates specific behavioral and synaptic phenotypes, highlighting their potential neuroprotective role in neurodevelopmental disorders. This work supports the utility of Drosophila as a powerful model for studying gene–environment interactions relevant to ASD.

Funding: FONDECYT Iniciación en Investigación N°11230539

Deciphering Key Properties of Prion Replication Through PrP Mutagenesis

Carola Munoz-Montesino[1,2], Human Rezaei[2]

(1) Universidad de Concepcion, Departamento de Fisiología, Facultad de Ciencias Biológicas, Barrio Universitario, Concepcion, Chile
(2) INRAe, MAP2, Virologie et Immunologie Moleculaire, Jouy en Josas, Jouy en Josas, France

Transmissible spongiform encephalopathies are caused by the conversion of a normal CNS associated protein, Prion protein (PrPC), into a protease-resistant and pathogenic form (PrPSc). To understand mechanism of conversion most studies have been focused on the protease resistant domain, which contains 3 alpha helices in PrPC that convert into beta-strand in the PrPSc. Here, to further characterized the relevance of this domain, we engineered a series of PrP mutants harboring deletions within the H2-H3 region and assessed their impact on prion conversion and replication. Mutants were expressed in cell lines and were evaluated using biochemical assays, including protease resistance profiling, conformational stability analyses, and prion amplification techniques.

Removal of residues at the C-terminal end of H2 did not impair prion replication. Instead, these deletion mutants supported efficient conversion into PrPSc and sustained prion propagation in vitro and in vivo. Notably, among the mutants, a 7 amino acid deletion induced spontaneous PrP conversion into the resistant form, which was capable of templating the conversion of the PrP C1 fragment—a cleavage product generally considered conversion-incompetent.

These results indicate that the C-terminal segment of H2 is not strictly required for prion replication. However, this alterations increased the ability of the protein to acquire the resistant form, and therefore, support the notion that this segment limits PrP conversion. This finding challenges structural models that assign an essential role to this H2 region in prion conversion and suggests that this region might be relevant to control conversion in this disease. 8

Targeting IGF2 Signaling for Immune Modulation of Microglia in Parkinson's Disease

René L. Vidal[1,2,3], Tomas Huerta[1,2], Valentina Urra[1,3], Cathalina Marin[1], Valentina Urbina[1], Tomas Contreras[1,3], Francisca Cornejo[1]

(1) Universidad Mayor, Centro de Biología Integrativa, Ciencias, Camino La Piramide 5750, Santiago, Chile
(2) Center for Geroscience, Brain Health and Metabolism, Santiago, Chile
(3) Universidad Mayor, Escuela de Biotecnologia, Ciencias, Camino La Piramide 5750, Santiago

Objective: We propose that IGF2 induces a distinct inflammatory phenotype in macrophages or microglia derived from Parkinson's disease (PD) patients.

Background: Microglia are the resident immune cells of the central nervous system, responsible for sensing and responding to pathological stimuli, thereby promoting an inflammatory response known as neuroinflammation.Recent studies indicate that insulin-like growth factor 2 (IGF2) exerts immunomodulatory effects on peripheral macrophages through epigenetic remodeling via the IGF2/IGF2 receptor (IGF2R)/GSK3β axis. However, the role of IGF2 in microglial immune regulation in PD remains poorly understood.

Methods: Primary microglial cultures or microglia derived from peripheral blood mononuclear cells (PBMCs) of PD patients were treated with IGF2. The inflammatory profile of microglia was assessed via quantitative PCR (qPCR) to evaluate the gene expression of pro-inflammatory markers, including TNF-α, and anti-inflammatory markers, including IL-10 and Nurr1. Additionally, immunofluorescence analysis was performed to assess the nuclear translocation of IGF2R and GSK3β.

Results: Our findings indicate that IGF2 modulates microglial migration and promotes an anti-inflammatory phenotype in a time- and dose-dependent manner. This suggests that IGF2 plays a critical role in shaping the microglial inflammatory response.

Conclusion: IGF2 regulates the inflammatory response of microglia by upregulating the expression of anti-inflammatory markers. These findings highlight the potential of IGF2 as an immunomodulatory molecule in the neuroinflammatory processes associated with PD.

Funding: Support provided by Fondecyt N° 1230980 (R.L.V.). Additional support was received from the FONDAP Program N° 15150012 (R.L.V.), and the Doctoral ANID Fellowship N° 21240735 (T.J.H.).

AMPK regulates BK-channel current in CA1 hippocampal neurons

Ricardo Felipe Esquivel Garcia[1], Jorge Bravo Martinez[1], Karina Bermeo Mora[1], Isabel Arenas Reyes[1], David Erasmo García Diaz[1]

(1) Universidad Nacional Autónoma de México, Fisiologia celular, Medicina, Avenidad Universidad 3000, Ciudad de México, México

AMP-activated protein kinase (AMPK) is a fundamental energy sensor that fine-tunes cellular activity according to ATP availability. BK-channel current is modulated by leptin, which in turn regulates neuronal excitability, although the underlying mechanism remains unclear. Here, we aimed to determine whether AMPK mediates leptin regulation of BK-channels.

We hypothesized that AMPK mediates the effects of leptin on BK-channels, thereby modulating the excitability of CA1 hippocampal neurons. Using hippocampal slices, patch-clamp recordings from CA1 pyramidal neurons, and pharmacological tools, we found that AMPK activation with AICAR inhibits BK-channel current, whereas AMPK inhibition with Compound C enhances it. Remarkably, AMPK activation reverses the leptin-induced enhancement of BK-channel current, supporting an AMPK-dependent metabolic regulation of BK-channels. Consistently, current-clamp experiments revealed that AMPK manipulations significantly influence leptin-induced changes in CA1 neuronal firing. These findings identify AMPK as a key mediator of the interplay between leptin and neuronal excitability in the hippocampus, integrating metabolic signals with the firing dynamics of CA1 pyramidal neurons.

Funding: Supported by UNAM-DGAPA-PAPIIT: IN210325

ORAL COMMUNICATIONS II

Chairs: Christ Devia and Marco Fuenzalida

Bidirectional control of cortical activity by chandelier interneurons

Alejandre-Garcia Tzitzitlini[1], Rafael Yuste[1]

(1) Neurotechnology Center, Columbia University, Biological Sciences, NY 10027, New York, USA

The inhibition-excitation synergy of neuronal ensembles is important for visual perception. Chandelier cells (ChCs) are an anatomically distinct class of interneurons that innervate pyramidal cells at their axon initial segments, where action potentials are generated. This suggests that a single ChC could influence the activity of hundreds of local pyramidal neurons. We are exploring the effects of activating ChCs in the local cortical network, and have found that that, differently from other GABAergic interneurons, ChCs have a dual effect on cortical neurons: they excite them at rest but inhibit them when they are activated. Our results show that ChCs dynamically balance the activity of cortical neurons, preserving a stable operating regime while preserving its dynamical response to visual stimulus.

Funding: Supported by NINDS (RM1NS132981), NEI (R01EY035248), NIMH (R01MH115900), Ikerbasque Foundation and Secretaria de Educacion, Ciencia, Tecnologia e Inovacion de la Ciudad de Mexico (SECTEI).

Behavioral and proteomic characterization of a mouse model of binge eating disorder: intermittent palatable food exposure enhances compulsive-like behavior

Paula Acevedo-Hernández[1], Wladimir Plaza[4], Ute Woehlbier[2], Pablo Moya[3,4]

(1) PhD Program in Science mention Neuroscience, Universidad de Valparaíso, Valparaiso, Chile
(2) Center for Integrative Biology, Universidad Mayor, Santiago, Chile
(3) Centro de Estudios Traslacionales en Estrés y Salud Mental (C-ESTRES), Universidad de Valparaíso, Valparaíso, Chile
(4) Institute of Physiology, Faculty of Science, Universidad de Valparaíso, Valparaiso, Chile

Background: Binge eating disorder (BED) is characterized by recurrent episodes of unusually large amounts of food consumption. Its increasing global prevalence has been linked to heightened anxiety-related eating behaviors and greater access to palatable foods, contributing to diminished quality of life. However, research on BED's neurobiological mechanisms remains limited. This study aimed to explore molecular alterations in the hypothalamus of a mouse model potentially involved in BED predisposition.

Methods: Female C57BL6J Wildtype mice (Day 30–40) were divided into three groups: Control without exposure (Control S/E), Control with continuous exposure to palatable food (Control E/C), and Intermittent exposure group (Binge). For 30 days, Binge animals had 2-hour access to palatable food every other day. Behavioral tests assessing anxiety and compulsivity-like behavior were performed. Hypothalami were obtained from Control E/C and Binge groups and analyzed by proteomics using LC-MS/MS. Proteins were identified with MSFragger v4.1; statistical analysis was performed in GraphPad Prism 9.

Results: The Binge group consumed more palatable food than Control E/C ($p<0.0001$). Behavioral differences included: Increased time spent in the center ($p<0.05$, elevated plus maze), less time in the light zone ($p<0.05$, light-dark box), longer average decision time to choose an arm ($p<0.05$, T-maze), and more burying behavior ($p<0.01$, marble burying test). Proteomic analysis identified 5,939 proteins, with 173 showing significant differences ($p<0.05$) between groups, related to GABAergic pathways, inflammation, and metabolism, among others.

Conclusion: Intermittent access to palatable food increases anxiety- and compulsive-like behaviors and is associated with hypothalamic molecular alterations, supporting further research into BED neurobiology.

Funding: Project FONDECYT 1231012 P.R.M.PhD fellowship 21221732, ANID.

Temporal Dynamics of Autonomic and Brain Sensory-Motor Resonance: A neurophenomenological study.

Alejandro Troncoso[1,2], Vicente Soto[1], David Martínez-Pernía[1], Antonia Zepeda[1], Gaspar Perello[1], Joel Álvarez-Ruf[3,4,5]

(1) Centro de Neurociencia Social y Cognitiva, Universidad Adolfo Ibáñez, Santiago, Chile;
(2) Escuela de Kinesiología, Facultad de Ciencias de la Rehabilitación y Calidad de Vida, Universidad San Sebastián, Valdivia
(3) Laboratorio de Cognición y Comportamiento Sensoriomotor, Departamento de Kinesiología
(4) Centro de Desarrollo de Investigación, Universidad Metropolitana de Ciencias de la Educación, Santiago, Chile;
(5) Laboratorio de Biomecánica Clínica, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Carrera de Kinesiología, Santiago, Chile

Introduction: Bodily resonance, the experiential basis of feeling another's suffering, involves the body being affected through sensations and affective changes. At the neural level, it has been associated with sensorimotor cortex activation, particularly through mu-band suppression (8–13 Hz), in empathy-for-pain studies. However, this relationship has been studied mainly in non-interactive contexts with artificial stimuli. The present study aims to explore sensorimotor and autonomic brain responses linked to bodily resonance during face-to-face interactions, integrating temporal dynamics informed by subjective experience.

Methods: Twenty-eight participants took part in a 90-second live interaction in which an actor expressed emotional suffering. Mobile EEG, electrodermal activity, and heart rate were recorded. Micro-phenomenological interviews guided the temporal analysis of physiological data, focusing on mu-band power, electrodermal activity, and heart rate, in 3-second windows.

Results: Phenomenologically, participants identified a shared

moment of maximum resonance when the actor said: "I'm going to forget everything, even that Cecilia is my wife." This moment was described as emotionally intense, with sensations of tightness in the chest and throat, distress, and a strong sense of presence in front of the other. Physiologically, a significant mu-band suppression ($p<0.01$) and an increase in electrodermal activity ($p<0.05$) were observed compared to the neutral condition.
Conclusion: These findings show that bodily resonance is both a lived and physiological process, grounded in interactive empathic experiences.

Increased aversive memory in the inhibitory avoidance test in mice subjected to a model of postnatal stress

Karina Pereira Luduvico[1], Melania Santer[1], Gabriela Duarte Karasiak[1], Manuella Cardoso[1], Caibe Alves Pereira[1], Manuella Kaster[1]

(1) Federal University of Santa Catarina, Biochemistry, Center for Biological Sciences, Rua João Pio Duarte Silva, 241, Florianópolis, Brazil

The first years of an individual's life are a period during which physical, emotional, and cognitive development begins. Stressful experiences in childhood are known to be associated with the development of neuropsychiatric disorders. In this context, the objective of this study was to evaluate behavioral changes in offspring induced by a model of early postnatal stress, consisting of maternal separation and reduction of nest material in the perinatal period, combined with social isolation after weaning. The animals were obtained from the C56BL/6 colony of the Biochemistry Multisectoral Animal Facility at UFSC. The project was approved by the Ethics Committee on Animal Use (No. 5936230624). The offspring (n = 14; 6 males and 8 females) were separated from their mothers from postnatal day (PND) 10 to PND 17, for 4 hours per day. Furthermore, nest material was reduced by one-third. Weaning occurred on PND 21. The animals were also subjected to social isolation from PND 46 to 60. On day 62, they underwent the inhibitory avoidance test. The group subjected to maternal separation and social isolation showed greater latency in the inhibitory avoidance test 8 h after training compared to the control group. Bonferroni post-hoc analysis revealed a difference between the groups ($P<0.0001$). Therefore, the stressed offspring demonstrated increased aversive memory. Stress during the perinatal period affected the behavior of the pups and may generate greater susceptibility to stressors throughout life.

Funding: Financial support: CAPES, CNPq, and FAPESC.

Docosahexaenoic acid supplementation in the perinatal period prevents impairment of both social play and anxiety-like behavior in prepubertal rats fed with a high-fat diet.

Lorena Mercado López[1,2], Ignacio Alvear[4], Robinson carrasco[3], Rodrigo Valenzuela[2], Alexies Dagnino[3]

(1) Universidad Andrés Bello, Escuela de Nutrición, Medicina, Quillota 980, Viña del Mar, Chile
(2) Universidad de Chile, Nutrition, Medicina, Av.Independencia 1027, Santiago, Chile
(3) Universidad de Valparaíso, Institute of Physiology, Laboratory of stress neurobiology, Av.Gran Bretaña 1091, Valparaíso, Chile
(4) Universidad Santo Tomás, School of Nutrition and Dietetics, Faculty of Health, Ejercito libertador 146, Santiago, Chile

Introduction: Obesity is associated with an increased risk of chronic diseases and mood disorders. N-3 polyunsaturated fatty acids (n-3 PUFA), particularly docosahexaenoic acid (DHA), are critical for fetal brain development with deficiencies linked to anxiety and depression. Objective: To evaluate the effect of HFD with 2%DHA supplementation feeding in behavioral aspects (social play, anxiety-like and depression-like) in rats Sprague-Dawley through perinatal period.

Methods: Thirty-six female rats were divided into six groups (n=6) based on diet: control (CD), HFD, CD deficient in alpha-linolenic acid (CD 0.1% ALA), HFD 0.1% ALA, CD 2% DHA, and HFD 2% DHA. Diets were administered for 18 weeks, including mating, gestation, and lactation. Behavioral tests evaluated anxiety-like and depression-like behaviors, as well as social play in offspring. Metabolic and inflammatory markers, along with fatty acid profiles in tissues (erythrocytes, adipose tissue, liver and brain), were assessed post-mortem. Statistical analysis: two-way ANOVA and Pearson correlation were performed.

Results: i) DHA supplementation improved metabolic profiles in dams, reduced offspring inflammation and significantly increased DHA content in tissues. ii) Anxiety-like behavior decreased in DHA-supplemented dams ($p<0.05$). iii) Male offspring exposed to HFD or ALA-deficient diets exhibited impaired social play and anxiety-like behavior. iv) Anhedonia, observed only in female offspring, was prevented with DHA supplementation. v) n-3 PUFA maternal erythrocyte levels inversely correlated with anxiety index during pregnancy.

Conclusion: Male offspring were more vulnerable to metabolic stress from HFD during early life. DHA supplementation mitigates anxiety-like behaviors in both dams and male offspring, highlighting its protective effects during the perinatal period.

Funding: Acknowledgements: This research was supported by FONDECYT Regular 1221098. ANID BECAS/DOCTORADO NACIONAL 21220864.Conflict of interest: All authors declare no conflict of interest.

Cognitive Advantages in Teachers: A Behavioural Study of Metacognitive Efficiency and Cognitive Flexibility

Consuelo Soto[1,3], Ivo Leiva[2], Paulo Barraza[1,2]

(1) Universidad de Chile, Institute of Advanced Studies in Education (IE), Periodista José Carrasco Tapia #75, Santiago, Chile
(2) Universidad de Chile, Centre for Advanced Studies in Education (CIAE), Periodista José Carrasco Tapia #75, Santiago, Chile
(3) Universidad de Chile, Faculty of Social Sciences (FACSO), Capitán Ignacio Carrera Pinto 1045, Santiago, Chile

Teaching in the educational context is a highly demanding and complex task. It has been proposed that the teaching ability deployed by teachers may encompass the development of specific cognitive skills. Prior research suggests that teaching in school settings frequently engages metacognition and cognitive flexibility,

which would allow teachers to continuously monitor and adapt their cognitive and behavioural strategies during instruction. However, whether the development of these higher-order capabilities markedly differs between teachers compared to other professionals remains an open question. To address this issue, the metacognitive efficiency (Meta d'/d') and set shifting/cognitive flexibility (Perseverative errors) of a group of teachers and a control group of professionals from other fields were assessed by means of two behavioural tasks (Two-Alternative Forced-Choice Metamemory Task and the Wisconsin Card Sorting Test). Results showed that both metacognitive efficiency (Meta d'/d') and cognitive flexibility (Perseverative errors) were significantly better for the group of teachers when compared to the control group. Together, these findings provide empirical support for the hypothesis that long-term engagement in teaching within school settings may foster cognitive adaptations, namely metacognitive efficiency and set shifting/cognitive flexibility. The implications of these findings for the understanding of the teaching ability, teacher education, further venues of research, and cooperation between the cognitive neurosciences and education are discussed.

Funding: This work was supported by grants FONDECYT 1201443; the PIA-CONICYT Basal Funds for Centers of Excellence Project FB0003; and the ANID Support 2024 AFB240004.

Attentional set-shifting task: an approach to assess prefrontal activity patterns during cognitive flexibility in aged mice.

Francisca Javiera García Rojas[1], Pablo Fuentealba[2], Wael El-Deredy[3], Ignacio Negrón[1]

(1) Universidad de Valparaíso, Instituto de Fisiología, Facultad de Ciencias, Valparaíso, Chile
(2) Pontificia Universidad Católica de Chile, Facultad de Medicina, Santiago, Chile
(3) Universidad de Valparaíso, Facultad de Ingeniería, Valparaíso, Chile

Normal aging is characterized by a decline in several cognitive faculties, including the ability to adapt behavior in response to changing environmental contingencies. The impairment of this ability, known as cognitive flexibility (CF), has been associated with the disruption of neural systems underlying CF, including the medial prefrontal cortex (mPFC) and the hippocampus (HPC). However, it remains unclear how oscillatory brain activity in the mPFC and the HPC relates to impaired CF in aged mice.
CF can be assessed using the Attentional Set-Shifting Task (ASST). In this task, rodents learn to associate either the odor or the texture of a digging pot as a relevant cue to locate a buried reward. Here, we performed simultaneous recordings of neural activity and local field potential (LFPs) in the mPFC of adult and aged mice during the ASST.

We found that adult mice completed the full task (six stages) and successfully learned to attend to the relevant cue (digging medium) while ignoring the irrelevant one (odor), by consistently associating the reward with the digging medium. Conversely, aged mice were unable to complete the entire task and required more trials to reach the criterion in individual stages. Additionally, aged mice made more errors and took longer to complete each trial compared to adult mice.
We are currently analyzing in vivo single-unit and LFP data collected during the ASST, to evaluate the synchronization of neural activity patterns along HPC/mPFC axis. This research aims to elucidate the neurophysiological alterations associated with CF decline in aging.

Funding: Fondecyt postdoctoral N° 3230400.

The Preprocessing Bias: Methodological Drivers of Synergy–Redundancy Detection in Cortical Microcircuits

Sebastián Orellana-Villota[1,2], Salvador Dura-Bernal[3,4], Patricio Orio[1,2]

(1) Universidad de Valparaíso, Ciencias, Ciencias, Av. Gran Bretaña 1091, Playa Ancha, Valparaíso, Chile
(2) Centro Interdisciplinario de Neurociencia de Valparaíso (CINV), Ciencias, Ciencias, Pasaje Harrington 287, Playa Ancha, Valparaíso, Chile
(3) SUNY Downstate Health Sciences University, Physiology and Pharmacology, Medicine, 450 Clarkson Avenue, Brooklyn, New York, United States
(4) Nathan Kline Institute for Psychiatric Research, Center

Transforming discrete spike times into continuous firing rates is a fundamental step in computational neuroscience. However, preprocessing choice can critically influence High-Order Statistics (HOS) methods such as O-information, which detects the balance of synergy—information emerging from joint interactions beyond individual contributions—and redundancy, where elements convey similar information— between neural elements.
We investigated these effects using a Potjans–Diesmann microcircuit model implemented in NetPyNE, comprising over 7,000 excitatory/inhibitory integrate-and-fire neurons across 4 cortical layers, simulated for 30s. HOS analysis was applied to the average firing rates of each population (8 signals), extracted using Gaussian/Alpha kernel smoothing and other ISI-adaptive methods. O-information was computed between population signals at different interaction orders (n>2 combinations of signals), using two complementary estimators: Gaussian-Copula (GC), primarily sensitive to linear dependencies, and Kraskov–Stögbauer–Grassberger (KSG) k-nearest-neighbor, which captures both linear and nonlinear interactions. Statistical significance was established via Z-scores against phase-randomization and time-shift surrogates. Preliminary results showed that signal over-smoothing suppressed high-frequency dynamics and underestimated synergy, while adaptive methods preserved more temporal richness, revealing a shift from synergy at lower interaction orders to redundancy at higher ones. Under phase-randomization, GC yielded large redundancy Z-scores increasing with interaction order, reflecting heightened sensitivity to accumulated linear correlations. KSG detected lower-magnitude, more balanced synergy/redundancy interactions, remained stable across interaction orders, and exhibited stronger nonlinear sensitivity under time-shift surrogates. By uncovering how preprocessing, and estimator choice, shape the synergy–redundancy landscape, this work provides methodological guidance for robust HOS analysis and deepens insight into how cortical microcircuits integrate and distribute information—linking neural architecture with emergent dynamical features.

Fondecyt Regular 1241469, Centro Basal AC3E (FB0008) and ANID Doctorado Nacional 2024 Folio 21241572 (Chile).

Alpha-Based EEG Brain Clocks Reveal the Impact of Neurodegeneration and Social Inequality on Brain Aging

Pavel Prado[1], Mónica Otero[2], Felipe Carriel[3], Hernán Hernández[4], Agustín Ibáñez[4]

(1) Universidad San Sebastián, Escuela de Fonoaudiología, Facultad de Ciencias de la Rehabilitación y Calidad de Vida, Santiago, Chile
(2) Universidad San Sebastián, Facultad de Ingeniería, Santiago, Chile
(3) Universidad San Sebastián, Doctorado en Biología Computacional, Santiago, Chile
(4) Universidad Adolfo Ibañez, Latin American Brain Health Institute (BrainLat), Santiago, Chile

Brain age models estimate an individual's biological brain age based on neurophysiological data, providing a non-invasive measure of functional brain aging. The difference between predicted brain age and chronological age—known as the brain age gap (BAG)—has emerged as a promising biomarker of neurological decline. This international and multicentric study investigated whether BAG, when derived from resting-state electroencephalographic (rsEEG) α-oscillations, captures neurodegenerative processes and reflects sociodemographic diversity and structural inequality. BAG was computed using spectral descriptors of α-activity in the source space of rsEEG recordings from 1,228 individuals, including healthy participants, individuals with mild cognitive impairment (MCI), and patients with Alzheimer's disease or behavioral variant frontotemporal dementia, residing in ten countries across Latin America and Europe with different levels of structural inequality (Gini index, as reported by the World Bank). BAG was significantly elevated in individuals with MCI and dementia, especially in posterior cortical regions. Notably, BAG also increased with higher levels of structural inequality among cognitively healthy individuals. Among all examined variables, structural inequality emerged as the strongest predictor of BAG, surpassing cognitive performance, educational attainment, and sex. These findings demonstrate the sensitivity of α-based brain clocks to both neurodegenerative and social factors that influence brain aging. They also underscore the importance of incorporating structural context into brain health research, particularly for understanding vulnerability in underrepresented and socioeconomically diverse populations.

POSTER SESSION I

Characterization and visualization of nanostructures in intact mouse brain tissue using expansion microscopy and two-photon imaging.

Javiera Villouta[1], Tomás Osorio[1], Ale Frene[1], Victor Hugo Cornejo[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Av. Libertador Bernardo O'Higgins 340, Santiago, Chile

At the cellular and molecular level, the neuronal circuits that form the brain remain only minimally deciphered. Resolving nanometer-scale structures within large tissue volumes is hindered by the diffraction limit of light microscopy. For analyzing the morphology and internal content of synaptic nanostructures such as dendritic spines, super-resolution microscopy is often employed. However, these systems produce only superficial imaging, requiring very thin brain sections, which sever neuronal projection and preclude volumetric analysis. In recent years, expansion microscopy (ExM) has emerged as a powerful strategy to overcome this limitation by physically magnifying tissues using hydrogels, achieving up to a fourfold or greater linear increase in three dimensions. This physical magnification enhances resolution and allows to visualize molecules associated to synaptic compartments. Combining ExM with two-photon microscopy offers the advantage of imaging at greater depths in thick samples, allowing both nanoscopic and volumetric analysis. We implemented ExM on coronal sections of mouse brain expressing fluorescent markers, as well as on sections processed with immunofluorescence. Samples were embedded in a polymer gel, which was expanded through successive immersions in aqueous solutions and imaged using two-photon microscopy. This approach enabled precise measurement of the size of dendritic spines, thereby facilitating the extraction of ultrastructural features, specially the spine neck volumes. By integrating this methodology, it becomes possible to directly correlate in vivo neuronal function with ultrastructural features, providing new insights into the structure-function relationships of brain synapses.

Funding: FONDECYT 11230291, FONDEQUIP EQM240080 and Programa PIA UC

Lactate dynamics modulated by MCT1 and glucose oxidation shifts in age-related energy decline in the corpus callosum

Gonzalo Mayorga-Weber[1], Pablo Alarcón[2], Gaspar Peña-Münzenmayer[1,3], Patricio Rojas[4], Rafael A. Burgos[2], Francisco J. Rivera[5], Maite A. Castro[1]

(1) Universidad Austral de Chile, Instituto de Bioquímica y Microbiología, Facultad de Ciencias, Valdivia, Chile
(2) Universidad Austral de Chile, Institute of Pharmacology and Morphophysiology, Faculty of Veterinary Sciences, Valdivia, Chile
(3) Universidad Austral de Chile, Núcleo de Innovación en Biotecnología Apícola (NIBApi), Valdivia, Chile
(4) Universidad de Santiago, Departamento de Biología, Santiago, Chile
(5) University of Helsinki, Molecular and Integrative Biosciences Research Program (MIBS), Faculty of Biological and Environmental Sciences, Helsinki, Finland

The global population is aging, as reported by the World Health Organization (WHO). The brain, an energy-dependent organ, experiences a significant decline in energy production as we age. The corpus callosum, a major white matter tract, undergoes changes in energy metabolism during aging that remain poorly understood. This study aimed to investigate axonal energy metabolism in the corpus callosum and the potential role of Monocarboxylate Transporter 1 (MCT1) in age-related metabolic alterations. We analyzed the corpus callosum of young (3-4 months) and aged (18-24 months) mice, focusing on metabolic changes. Metabolomic analysis by gas chromatography-mass spectroscopy (GC-MS) revealed lactate accumulation, reduced glucose levels, and oxidative stress in aging. Neuronal stimulation experiments using SoNar fluorescent sensor demonstrated a reduced capacity for oxidative energy metabolism in aged axons, evidenced by a lower axonal NADH/NAD+ ratio during electrical stimulation. In young axons, oxidative energy metabolism is sustained by glycolysis, lactate production, and lactate transport mediated by MCTs during electrical stimulation. However, these processes are significantly impaired in aged axons. Additionally, glucose oxidation shifted preferentially to the pentose phosphate pathway (PPP) during electrical stimulation, highlighting its role in mitigating oxidative stress in aging. We observed reduced lactate uptake and MCT1 expression in aging. This reduction likely disrupts lactate flux and oxidation, contributing to energy inefficiencies that may promote oxidative stress and axonal deterioration. Our findings emphasize the need for further investigation of the role of MCT1 and lactate metabolism as therapeutic targets to preserve white matter integrity and axonal function in the aging brain.

Funding: FONDECYT grant 1191620 (MAC), FONDECYT grant 1201706 (FJR), Sigrid Juslius Foundation gran (FJR), Janelia Visitor Program JSV0028700 (MAC), Chilean FONDEQUIP grant EQM 130257 (RAB), Nucleo NIBApi VIDCA UACh INED I+D ANID INID210009 (GPM).

Phosphorylation at Serine 29 Regulates TRPM8 Degradation

Elizabeth Mendoza Atuesta[1], Ana Gómez del Campo[1], Rodolfo Madrid Montecinos[1], María Pertusa Pastor[1]

(1) Universidad de Santiago de Chile, Biología, Facultad de Química y Biología, 9160000, Santiago, Chile

In mammals, cold detection by peripheral cold thermoreceptor neurons (CTNs) primarily relies on TRPM8, a polymodal TRP channel activated by cold, menthol, voltage, and increased osmolality. Several mechanisms, including phosphorylation, tightly regulate TRPM8 function. We previously identified phosphorylation at serine 29 as a key modification that downregulates TRPM8 function by reducing the number of active channels at the plasma membrane. To investigate how this post-translational modification governs TRPM8 surface expression, we generated stable HEK293 cell lines expressing either wild-type mTRPM8-myc or the non-phosphorylatable mutant S29A-mTRPM8-myc. Cells expressing the S29A channel showed enhanced responses to cold and menthol, associated with an increased maximum conductance and a leftward shift of the half-maximal activation voltage towards negative

membrane potentials. To explore whether this increase in Gmax is due to reduced degradation, we estimated the half-life of TRPM8 using cycloheximide (CHX), a protein synthesis inhibitor. The S29A mutation prolonged the channel's half-life and slowed its degradation under CHX treatment. Furthermore, lysosomal inhibition with chloroquine (CQ) and bafilomycin A1 (BafA1) showed that TRPM8 accumulates more slowly in lysosomes in the S29A mutant. This suggests that the dephosphorylation of S29 delays TRPM8 transport to the lysosomal compartment. Colocalization studies using LysoTracker in both wild-type and S29A-expressing cells will help further define the contribution of S29 phosphorylation to the regulation of TRPM8 trafficking toward lysosomes. Our findings underscore the role of S29 phosphorylation in regulating the cell TRPM8 expression levels, and should be considered when studying pathological conditions related to altered TRPM8 function.

Funding: Supported by FONDECYT 1241513 (MP and RM) and VRIIC-DICYT 022443MM (RM and MP). EM thanks the support of ANID fellowship 21232288.

A Biotin Ligase-Based Approach to Identify the TRPM8 Interactome

Florencia Alliende Paraud[1], David Necuñir[1], Elizabeth Mendoza[1], Rodolfo Madrid[1], María Pertusa[1]

(1) Universidad de Santiago de Chile, Departamento de Biología, Facultad de Química y Biología, Santiago, Chile

The TRPM8 channel is a critical component of the molecular machinery responsible for sensing cold temperatures in the somatosensory system. Cold, cooling compounds, voltage, and osmolality rises activate this polymodal thermo-TRP channel. TRPM8 modulation includes its phosphorylation at serine 29, which downregulates its function, decreasing cold- and menthol-evoked responses. However, the kinase responsible for this basal phosphorylation is still unknown. Given that the pharmacological approach using known kinase inhibitors proved ineffective to identify this kinase, we decided to employ a strategy based on a proximity-dependent biotin identification assay to avoid the limitations of traditional screening methods for identifying protein-protein interactions. To tag proteins vicinal to TRPM8 in intact cells, we engineered four constructs by fusing mutant biotin ligases from Escherichia coli and Aquifex aeolicus to either the N- or C-terminal domains of TRPM8. We assessed the expression levels of these constructs, examined their subcellular distribution by immunochemistry, and tested their functionality using Ca^{2+}-imaging to corroborate that the introduction of a biotin ligase does not affect the efficient targeting of the channel or its ability to be activated by its agonists, cold and menthol. All the constructs produced functional channels, similarly distributed as the wild-type channel. Finally, the proximity biotinylation assay revealed a putative set of proteins that interact with TRPM8. Our findings support the use of biotin ligase–fused TRPM8 constructs as a valuable tool to identify vicinal proteins potentially involved in the regulation of this ion channel.

Funding: Supported by FONDECYT 1241513 (MP and RM) and VRIIC-DICYT 022443MM (RM and MP). EM thanks the support of ANID fellowship 21232288.

Calcium Governs Dysferlin Migration to the Plasma Membrane

María José Guerra[1], Sissi Fuentealba[1], **Ana M. Cárdenas**[1]

(1) Universidad de Valparaíso, Centro Interdisciplinario de Neurociencia de Valparaíso (CINV), Facultad de Ciencias, Grand Bretaña 1111, Valparaíso, Chile

Dysferlin is a transmembrane protein with a large cytoplasmic N-terminus containing seven C2 domains. These domains bind Ca^{2+} and phospholipids. Mutations in the dysferlin gene cause dysferlinopathies, a group of muscular dystrophies characterized by progressive muscle weakness and atrophy. Skeletal muscle biopsies from patients with dysferlinopathy often show significantly reduced or absent dysferlin expression and sarcolemma discontinuities. Dysferlin's most accepted function is in sarcolemma repair. It appears to promote the aggregation and fusion of vesicles to form a membrane patch, resealing wounded membranes. In this study, we investigated dysferlin insertion into the plasma membrane under varying submembrane Ca^{2+} levels, using the DYSF2 cell line as a model. This cell line was derived from a patient biopsy with DYSF gene mutations leading to low dysferlin expression. We first compared the DYSF2 cells' ability to respond to different ionomycin concentrations with a submembrane Ca^{2+} signal, measured using pN1-Lck-GCaMP3 (a membrane-tethered GCaMP3) and TIRF microscopy. We observed that DYSF2 cells exhibited a Ca^{2+} signal pattern similar to C25 cells, a control cell line from a healthy individual's semitendinosus muscle biopsy. Next, experiments involved DYSF2 cells expressing dysferlin-pHluorin, stimulated with 20 µM ionomycin across extracellular Ca^{2+} concentrations ranging from 0 to 10 mM. Analyzing recruitment via TIRF microscopy, we found that 10 mM extracellular Ca^{2+} yielded maximum dysferlin recruitment. This highlights the critical role of Ca^{2+} in modulating dysferlin's function at the membrane and provides further insight into the mechanisms underlying sarcolemma repair, which is often compromised in dysferlinopathies.

Funding: FONDECYT 1220825

The epigenetic consequence of oxidative damage: 6-hydroxydopamine alters dopaminylation levels in the catecholaminergic PC12 cell line

Francisco Javier Novoa San Miguel[1], María Estela Andrés Coke[1], Jorge Campusano Astorga[1]

(1) Pontificia Universidad Católica de Chile, Biología Celular y Molecular, Ciencias Biológicas, Av. Libertador Bernardo O'Higgins 340, Santiago, Santiago, Chile

Parkinson's disease (PD) is a chronic neurodegenerative pathology characterized by progressive degradation of dopaminergic neurons in the substantia nigra (SN) and reduced dopamine levels in the striatum. While the etiology of the pathology has not been fully defined, alterations in histone 3 (H3) epigenetic marks such as methylations and acetylations have been described. Transglutaminase 2 (TG2) is an enzyme that catalyzes a posttranslational modification (PTM) of proteins called aminylation, formed by the covalent bond between a primary amine and a glutamine residue. Within the nucleus, TG2 is capable of covalently linking biogenic amines such as dopamine to glutamine 5 (Q5) of H3

process known as dopaminylation (H3Q5dop). TG2 has previously been found to have increased mRNA levels and enzymatic activity in the SN of human brains affected by PD. Due to epigenetic marks having a role in regulating PD-associated gene expression, dopaminylation could also have a role in disease progression, however, no work has described changes in its levels. This work's aim is to determine whether changes in dopaminylation levels occur after exposing the catecholaminergic cell line PC12 to 6-hydroxydopamine (6-OHDA), neurotoxin previously used to induce PD-like states in vitro and in vivo. Cells exposed to 0.02% ascorbic acid (AA) (vehicle) and 160 µM 6-OHDA exhibited increases in dopaminylation levels. This could suggest that H3 aminylation is involved in the evelopment of PD-like phenotypes. Future studies should focus on characterizing transglutaminase 2 localization and activity during early stages of PD.

Funding: Supported by Fondecyt 1231556. and PUENTE-2025-9 UC

Astrocyte-derived extracellular vesicles shape microglial synaptic phagocytosis triggered by Lipopolysaccharide from an oral pathogen

Antonia Figueroa Fritz[1], Pablo Lazcano[1], Daniela Corvalán[1], Javiera Gallardo[3], Úrsula Wyneken[1,2], Alejandro Luarte[2]

(1) Universidad de los Andes, Center for Biomedical Research, and Innovation (CiiB),, Medicine, Av. San Carlos de Apoquindo 2500, Santiago, Chile
(2) IMPACT, Center of Interventional Medicine for Precision and Advanced Cellular Therapy, Av. San Carlos de Apoquindo 2500, Santiago, Chile
(3) Universidad del desarrollo, Centro de Medicina Regenerativa, Medicina, Av. Plaza 680, Santiago, Chile

Astrocyte-derived extracellular vesicles (ADEVs) have recently emerged as key modulators of neuroinflammation, the brain's innate immune response. These vesicles carry regulatory molecules such as miR-26a, a microRNA known to counteract neuroinflammatory processes by repressing the expression of specific protein targets. Peripheral pathogens like Porphyromonas gingivalis (Pg)—an oral bacterium implicated in chronic periodontitis—and their virulence factors, including lipopolysaccharide (LPS), can trigger neuroinflammation by activating brain-resident microglia. In their overactivated state, microglia may aberrantly migrate and engulf synapses, contributing to neuronal injury. We hypothesize that ADEVs mitigate microglial phagocytosis induced by Pg-LPS through a mechanism dependent on miR-26a. Using the human microglial cell line HMC3, we investigated the effects of ADEVs on microglial engulfment of rat brain synaptosomes under LPS-induced neuroinflammation. We demonstrate that ADEVs significantly reduce synaptosome phagocytosis triggered by Pg-LPS. Moreover, manipulating miR-26a levels via mimic or inhibitor markedly alters the phagocytic response of microglia to LPS.We further identify Glycogen Synthase Kinase 3 beta (GSK-3β) as a downstream effector of miR-26a, linking this axis to the modulation of inflammatory microglial behavior.Together, these findings unveil a protective ADEV–miR-26a–GSK-3β axis that counteracts microglial overactivation and synaptic loss in response to periodontal pathogen signals.

Funding: Fondecyt regular 1240604Fondecyt Inicio 11220601

An Insular Perspective on the Neurobiology of Psychopathy: Vasopressinergic Modulation of Empathic Behavior in a Murine Model

Tomas Osorio Sanzana[1], José Luis Valdés[1,2], Marco Contreras[1,3]

(1) Universidad de Chile, Department of Neuroscience, Faculty of Medicine, Santiago, Chile
(2) Universidad de Chile, Biomedical Neuroscience Institution, Faculty of Medicine, Santiago, Chile
(3) University of Arizona, Department of Neuroscience, Bioscience Division, Tucson, USA

Psychopathy is a clinical construct associated with antisocial personality disorder, characterized by violent behavior, moral transgressions, and marked empathic dysfunction. Growing interest in this phenomenon has been driven by the sustained increase in premeditated violent crimes and the lack of effective therapies. One of the main challenges has been the limited understanding of the neurobiological mechanisms underlying this condition. Our research explored the role of vasopressin (AVP), a neuropeptide critically involved in the regulation of social behavior, in modulating neural circuits of the anterior insular cortex—a region implicated in interoceptive and affective integration as well as social decision-making. A murine model exhibiting prosocial behaviors analogous to human empathy was employed, and an operant task was used to assess the animals' capacity to act empathically in response to a conspecific in distress. Additionally, the behavioral impact of inhibiting vasopressinergic signaling was analyzed through bilateral administration of an AVP1a receptor antagonist into the anterior insula. This approach enabled the evaluation of the functional role of this circuit in the expression of empathic and psychopathic-like behaviors. Our results showed that vasopressinergic blockade selectively reduced empathic behavior in rats with high baseline levels of empathy, suggesting a functional limit to the inhibition of this circuit. These findings provide novel insights into the neurobiological mechanisms underlying psychopathy and propose the vasopressinergic insular cortex as a potential therapeutic target for its modulation.

Funding: Funding granted to Dr. José Luis Valdés (PhD) and Dr. Marco Contreras (PhD) for project #34503, titled "Understanding Psychopathy: How Vasopressin-Modulated Insular Circuits Regulate Empathic Behavior", Pew Innovation Fund, USA.

Mutations in mahjong gene cause Autism-like behavior in Drosophila melanogaster

Álvaro Monsalve-Gutierrez[1], Ana Luiza Bossolani Martins[2], Angelina Palacios Muñoz[1,3], Maria Rita Passos Buenos[4], John Ewer[1,5]

(1) Centro Interdisciplinario de Neurociencias de Valparaíso, Universidad de Valparaíso, Chile
(2) Universidade Federal de Mato Grosso do Sul, Paranaíba, MS, Brasil
(3) Laboratorio de Genética y Conducta, Facultad de Odontología, Universidad de Valparaíso, Chile

(4) Universidade de São Paulo, Instituto de Biociências, Centro de Estudos do Genoma Humano e Células-Tronco, Sao Paulo, SP, Brasil
(5) Instituto de neurociencias, Facultad de ciencias, Universidad de Valparaíso, Chile

This study investigated the function of the DCAF1 gene and its interaction with TRPC6, which are associated with Autism Spectrum Disorder (ASD) in humans. For this, we investigated the impact of mutations in their orthologs, *mahjong* and his interaction with previously described *trpy*, in *Drosophila melanogaster*, on courtship behavior (social interaction), grooming (repetitive/stereotyped behavior), and anxiety-like behavior. We also analyzed the expression of *mahjong* in the nervous system at different developmental stages. We found an increase in courtship behavior in mutant flies for both *mahjong* and *trpy*. While we observe a decrease in grooming index, hyperactivity and anxiety-like behavior in *mahjong* heterozygous mutant and *mahjong/ trpy* mutant animals. Histological analysis revealed mahjong expression in neuroblasts in the brain and the ventral nerve cord, during both larval and pupal stages, and in regions such as the mushroom bodies of the adult brain, suggesting a role in neurodevelopment and higher-order functions like memory and learning. These findings indicate that *mahjong* is involved in regulating behaviors that are analogous to core ASD symptoms, particularly in the social, repetitive sensorimotor, and anxiety-like domains. The interaction with trpy showed synergistic effects across these behavioral dimensions. Our results provide evidence that indicates that mahjong homolog DCAF1 gene is a risk factor for ASD, validating *Drosophila melanogaster.*

Nutritional adversity and vulnerability stress: an epigenetic model mediated by dFoxo in Drosophila melanogaster

Ivana Gajardo[1], Alvaro Glavic[1]

(1) University of Chile, Biology, Sciences, Pasaje Las Encinas 3370, Ñuñoa, Santiago, Chile

Nutrient availability and quality during critical developmental stages can shape the brain's epigenetic architecture, influencing social behaviors in adulthood. In Drosophila melanogaster, larval dietary alterations affect aggressive behaviors, yet the underlying molecular mechanisms remain poorly understood.
In this study, we combined profiles of chromatin accessibility (ATAC-seq) and gene expression (RNA-seq) to assess the impact of developmental nutritional restriction. We identified open chromatin signatures in regulatory regions of stress-related genes without concomitant transcriptional changes, suggesting a state of persistent epigenetic priming. Among these genes, we found evidence for regulation by the Drosophila forkhead transcription factor (FOXO), a known mediator of stress responses, indicating that dFOXO may contribute to abnormal behavioral responses to a second stressor in organisms previously exposed to nutritional adversity.

At the behavioral level, we assessed aggression in adult flies using a modified version of a classic assay. Nutritional restriction during development increased aggressive behavior in both sexes. This effect was further amplified in females exposed to an acute heat shock as a secondary stressor. Moreover, females with dFOXO knockdown exhibited reduced aggression compared to males, indicating a potential sex-dependent role for dFOXO in modulating aggressive responses under adverse conditions.

Together, these findings support a model in which dFOXO acts as a key integrator linking epigenetic programming to neural circuits underlying social behaviors, mediating behavioral sensitivity to stress in organisms with a history of early-life nutritional deprivation. This model provides a framework for exploring stress vulnerability and its molecular substrates within the neural circuitry of social behavior.

Funding: Supported by Millennium Institute Center for Genome Regulation #ICN2021-044 and FONDECYT #1231105

Game of neurons: metabolic cellular automata networks driving a vehicle in a virtual arena

Daniela Oviedo[2,3], Pedro Maldonado[2,4], Mircea Petrache[1,2], Alejandro Luarte[5]

(1) Pontificia universidad católica, Institute for Mathematical and Computational Engineering, Mathematics, Avenida Vicuña Mackenna 4860, Macul, Santiago, Chile
(2) National Center for Artificial Intelligence (CenIA), Santiago, Chile
(3) Universidad de Chile, Mathematical Engineering, Physical and Mathematical Sciences, Beauchef 851, Santiago, Chile
(4) Universidad de Chile, Neuroscience, Medicine, Av. Independencia 1027, Santiago, Chile
(5) Universidad de los Andes, Center for Biomedical Research and Innovation (CiiB), Medicine, Av. San Carlos de Apoquindo 2500, Santiago, Chile

Cellular Automata (CA) are a classical model of self-organizing systems with diverse emergent behaviors. They rely on a finite set of deterministic rules applied at each time step to indistinguishable nodes in a graph, where state updates depend on the local neighborhood. As seen in Conway's "Game of Life," varying the input state can lead to rich dynamical patterns. Here, we adapt this framework to simulate a toy neural network with energetic constrains coupled to a simple navigation task. The CA governs the behavior of a Braitenberg-like vehicle, enabling the model to become embodied.

This setup serves as a minimal model of a biological neural network, akin to a "brain in a dish." We define a discrete set of local rules representing neuron-like units and their interactions, inspired by biological principles such as spike-timing dependent plasticity, refractory periods, and energy constraints (metabolic CA).

Certain nodes receive input from the vehicle's sensors, while others produce motor outputs controlling its wheels. We investigate how the CA, embedded in a closed-loop sensorimotor system, generates emergent behavior while navigating the arena, with a special focus to the influence of metabolic dependencies over the emergent dynamics.

Funding: FONDECYT Exploración N° 13240026.

Neural correlates of ambiguity avoidance and management

Felipe Esteban Gómez Ibarra[1], Francisco Aboitiz[1], Rodrigo Henriquez[1], Pablo Billeke[2]

(1) Pontificia Universidad Católica de Chile, Centro de Investigaciones Medicas, Facultad de Medicina, Santiago, Chile
(2) Universidad del Desarrollo, Centro de Investigacion de Complejidad Social, Santiago, Chile

Every day, we make decisions without complete information, and these choices can profoundly shape our lives. Understanding how the brain processes uncertainty is key to explaining human behavior. Decision-making involves integrating sensory evidence, evaluating potential outcomes, and updating internal models of the world. Neuroimaging research has revealed distinct neural networks engaged during decision-making under risk (known probabilities) and ambiguity (unknown probabilities), indicating that different cognitive processes are recruited depending on the type of uncertainty.

Within this framework, two often overlooked mechanisms are ambiguity attitude, the preference for safety over ambiguity, and ambiguity management, the strategies used to act in ambiguous environments. We hypothesized that these are distinct cognitive processes with specific neural signatures: prefrontal activity linked to ambiguity attitude and parietal activity linked to ambiguity management, with prefrontal theta and parietal delta power modulations correlating with each process.

Thirty participants completed the Ambiguity Avoidance and Management task while EEG was recorded. Behaviorally, participants showed greater evasion under ambiguity than under risk, with avoidance increasing alongside ambiguity level. Ambiguity sensitivity correlated positively with obsessive–compulsive traits and neuroticism. EEG analyses revealed post-decisional frontal theta increases and pre-stimulus parietal beta decreases during safe choices, while ambiguity presence modulated frontal delta/theta and parietal beta activity.

These findings suggest that ambiguity avoidance engages a frontoparietal network with distinct temporal and spectral dynamics. Understanding these mechanisms advances our knowledge of the neurocognitive basis of uncertainty processing and may aid in identifying biomarkers for populations with heightened ambiguity sensitivity.

Retinal Structural Alterations and Their Association With Cognitive Impairment in Individuals Living With HIV

Maite Riquelme Quezada[1], Natalia Medina[1], Daniela Castillo[1], Iván Plaza Rosales[1,2]

(1) Universidad de Chile, Department of Medical Technology, Faculty of Medicine, Av. Independencia 1027, Santiago, Chile
(2) Universidad de Chile, Department of Neurosciences, Laboratorio de Neurosistemas, Faculty of Medicine, Av. Independencia 1027, Santiago, Chile

Background: Advancements in health-related scientific research on Human Immunodeficiency Virus (HIV) have led to documented epidemiological changes in the course of the disease. Specifically, the introduction of antiretroviral therapy (ART) has resulted in a global reduction in HIV-related mortality, transforming the infection into a chronic condition. Alongside the associated increase in life expectancy, new clinical challenges have emerged. Among these, the incidence of retinal alterations and their potential correlation with HIV-associated neurocognitive Disorders (HAND) has become a growing area of interest in both clinical practice and public health.. The primary objective of this study is to determine the relationship between retinal structural changes and cognitive impairment in individuals living with HIV. We hypothesize that the thinner the retina—whether in specific layers or overall structure—the lower the cognitive performance in people living with HIV.

Methods: Participants in our study will be classified into two groups (individuals living with HIV and healthy HIV-negative controls). All subjects will undergo an analysis of retinal parameters using Optical Coherence Tomography (OCT), and an assessment of their cognitive performance through neurocognitive tests adapted and validated for the Chilean population (IFS-Ch, ACE-III). Data will be analyzed using linear regression modeling, descriptive statistics, and group comparisons.

Results: We expect to find a greater magnitude of structural alterations in the retina in people living with HIV who perform poorly on cognitive tests.

Conclusion: This study proposes a non-invasive screening, diagnostic, and monitoring strategy that allows periodic assessment of cognitive changes in individuals living with HIV through the analysis of retinal structure.

Importance of the kugelei protein in the generation of behavioral phenotypes of Drosophila melanogaster

Kevins Jara Medina[1,2], Jorge M Campusano[2], Evelyn Avilés[2]

(1) Pontificia Universidad Católica de Chile, Medicine, Medicine, Ave. Libertador Bernardo O'Higgins 340, Santiago, Chile
(2) Pontificia Universidad Católica de Chile, Cellular and Molecular Biology, Biological sciences, Ave. Portugal 49, Santiago, Chile

Atypical cadherins of the FAT family, such as FAT3 and its Drosophila melanogaster ortholog, Kugelei, are actively involved in the organization and maintenance of neuronal circuits. Although the role of these proteins in nervous system development has been described, their function in adulthood, particularly in behavioral regulation, remains insufficiently explored. In this work, we evaluated the effect of homozygous mutations in kugelei on the locomotor behavior of adult flies and their survival. We used circular plate locomotion assays to characterize behavioral phenotypes associated with the functional loss of kugelei. Our preliminary results indicate that the mutant flies present a significant alteration in the total distance traveled and in exploration patterns compared to wild-type controls, which differ between females and males. These findings support the hypothesis that Kugelei is not only relevant for early neuronal development but also plays a key role in the functional maintenance of adult-related circuits throughout adulthood. This study contributes to a broader understanding of the conserved functions of Kugelei proteins in behavioral regulation, with potential implications for models of

neuropsychiatric disorders associated with altered neuronal connectivity.

Funding: UC VRI scholarshipJorge Campusano "Fondecyt" 1231556 and Evelyn Avilés "Fondecyt de iniciación" 11241253

Observational maternal stress affects oxytocin receptor expression and cellular immunomarkers of inflammation in the hippocampus of adult offspring

Robinson Carrasco Gutiérrez[1,2,3], Andrew Justin Taylor[2,3], Pablo R. Moya[4], Alexies Dagnino-Subiabre[2]

(1) Programa de Magíster en ciencias biológicas con mención en neurociencia, Universidad de Valparaíso, Chile
(2) Laboratorio de Neurobiología del estrés, Facultad de Ciencias, Universidad de Valparaíso, Gran Bretaña 1111, Valparaíso, Chile
(3) Programa de doctorado en ciencias con mención en neurociencia, Universidad de Valparaíso, Chile
(4) Laboratorio de neurogenética, Instituto de fisiología, Facultad de Ciencias, Universidad de Valparaíso, Gran Bretaña 1111, Valparaíso, Chile

One of the most stress susceptible periods of life is the perinatal period, alterations during this period can have long-term consequences for the offspring and the dam. A recently developed model in our lab of observational maternal stress in rats has allowed us to investigate the long-term effects of indirectly stressed mothers on the offspring. On postnatal day (PND) 3, the dam and pups on their homecage observed a social defeat stress session (SDS) between two male rats. Each SDS session lasted 30 minutes and was repeated for 7 days. In adulthood, the female and male offspring (PND 110) were assessed for anxiety-like and social behaviors. Immunofluorescence for the oxytocin receptor, the ionized calcium-binding adaptor molecule IBA-1, and glial fibrillary acidic protein GFAP revealed that maternal observational stress can generate long-term alterations in the offspring's hippocampus. These results suggest that maternal observational stress can generate alterations in neuroinflammatory processes during adulthood, in addition to altering systems strongly involved in social interaction, such as the oxytocinergic system.

Funding: Programa de magíster en ciencias biológicas con mención en neurociencia Universidad de Valparaíso, Puente-UV Grant Nº UVA20993 & CUECH RED21993

Bridging the Gaze: A Comparative Analysis of Human and Machine Visual Exploration in Reasoning Tasks

Samuel Madariaga[1,2], Amanda Silva[1], Christ Devia[1,2]

(1) Universidad de Chile, Departamento de Neurociencia, Santiago, Chile
(2) Centro Nacional de Inteligencia Artificial (CENIA, Santiago, Chile

Modern artificial intelligence models have achieved remarkable performance in visual reasoning tasks, yet their internal decision-making processes often remain opaque, differing significantly from human cognition. This exploratory study, aims to bridge this gap by conducting a direct comparative analysis between human visual exploration strategies and the internal mechanisms of visual reasoning machines.
We presented a shared set of complex visual stimuli and associated questions to both human participants and a state-of-the-art AI model. Human ocular behavior, including saccades and fixations, was recorded using high-fidelity eye-tracking to capture overt attentional patterns during the reasoning process. These gaze patterns were then systematically contrasted with the AI's internal attention maps, which highlight the image regions the model deems most relevant for generating an answer.

The core of this investigation focuses on identifying and characterizing the key disparities in these exploration strategies. We analyze whether the machine's approach is systematic or heuristic compared to the context-driven, goal-oriented gaze patterns observed in humans. This initial contrast seeks to uncover fundamental differences in how information is sampled and integrated. Ultimately, this research provides insights for developing next-generation "behavior-in-the-loop" systems, where understanding human-like visual exploration can lead to more robust and interpretable AI models.

Funding: The National Center for Artificial Intelligence CENIA, Chile (FB210017)Fondecyt iniciación (11241551)

The Effect of Ideological Beliefs on Emotional Responses to Police Violence: A Pilot Study

Romina Ortiz Hidalgo[1], Nicolle Espinoza[1], Millaray Carmona[1], Génesis Rojas[1], Marcos Domic[1], Joaquín Bahamones[1]

(1) Universidad Católica del Norte, Escuela de Psicología, Facultad de Humnanidades, Av Angamos 0610., Antofagasta, Chile

In recent years, empirical research on the impact of political ideologies on emotional responses has experienced notable growth, forging increasingly strong links between social psychology and neuroscience. Within this framework, it becomes crucial to understand how system justifying beliefs shape emotional reactions, perpetuating narratives that either minimize the severity of violent acts or, conversely, intensify indignation toward them. This study aligns with this line of research and examines the moderating role of political ideologies such as Right-Wing Authoritarianism (RWA), Social Dominance Orientation (SDO), and System Justification (SJ) on emotional reactions to violence-related stimuli.
Brain activity was recorded from n=30 adults using electroencephalography (EEG) while they viewed violent stimuli, focusing on the analysis of the Late Positive Potential (LPP) component. Changes in pupil dilation were measured via eye-tracking, and the Self-Assessment Manikin (SAM) was used to collect self-reported ratings of emotional valence and arousal.

Positive correlations were observed between SJ, SDO, and RWA and both emotional arousal and pupil dilation in response to violent stimuli, particularly when the violence was perpetrated by police forces. In contrast, negative correlations were found regarding subjective valence in response to violence against police officers, indicating greater emotional displeasure in such contexts. Furthermore, individuals with high levels of SDO and RWA exhibited reduced pupillary reactivity, while those with elevated scores in RWA and SJ showed decreased LPP amplitudes under violent conditions.

These findings suggest that political ideologies significantly influence emotional responses to scenes of violence.

Keywords:Police Violence; System Justification Theory; Social Domination Orientation; Right-Wing Authoritarianism; Late Positive Potential.

Funding: National Agency for Research and Development (ANID): FONDECYT REGULAR 1250393; FONDEQUIP 230003 Exploration Project #13220187 Legitimacy of the police in Chile: the causal effect of violence and corruption from a multi-actor, longitudinal, and multi-method perspective.

Effects of Resistance Training on Cognition and physical performance in Older Adults with Mild Cognitive Impairment after 12 Weeks of Intervention Compared to Usual Care

Paulina Sepúlveda Figueroa[1], Teresa Castillo[3], Valeria Oporto[1], Alexis Sepúlveda[2], Gabriel Marzuca[2]

(1) Universidad de La Frontera, Ciencias Preclínicas, Medicina, Claro 115, Temuco, Chile
(2) Universidad de La Frontera, Ciencias de la Rehabilitación, Medicina, Claro Solar 115, Temuco, Chile
(3) Universidad de La Frontera, Especialidades Médicas

Mild cognitive impairment (MCI) is an intermediate stage between normal aging and dementia, representing a key window for implementing preventive strategies. Evidence has shown that reduced muscle strength is associated with a higher risk of developing dementia, and resistance training has emerged as a promising non-pharmacological intervention to preserve cognitive function.

This study aimed to compare the effects of progressive resistance exercise versus usual therapy on cognitive function and physical performance in older adults with MCI. This is an ongoing randomized controlled trial. Here, we present preliminary results from 20 individuals over the age of 60, diagnosed with MCI using the MoCA and PFAQ, and recruited from the community. Participants were randomly assigned to a control group (usual therapy: educational talks) or an intervention group (usual therapy plus supervised resistance training three times per week for 12 weeks). Cognitive function (ACE-III) and physical performance (TUG) were assessed, and t-tests and repeated measures ANOVA were applied.

After 12 weeks, the intervention group showed significant group*time interactions in total ACE-III scores ($p = 0.029$) and attention ($p = 0.038$), with improvements in the intervention group. Memory showed a time effect ($p = 0.010$), with improvements in both groups. Verbal fluency also showed a significant interaction ($p = 0.036$), though post hoc results were not significant. TUG scores improved over time ($p < 0.001$) and showed a significant interaction ($p = 0.004$), favoring the intervention group.

These preliminary findings suggest that resistance training may effectively enhance cognition and physical function in older adults with MCI.

Neuronal activity in the medial prefrontal cortex and lateral hypothalamus during compulsive palatable food consumption in a mouse model of binge eating

Astrid Muñoz Pérez de Arce[1], Pablo Moya[2,3], Ignacio Negrón-Oyarzo[2]

(1) Programa Doctorado Ciencias Biológicas, mención Neurociencias. Facultad de Ciencias. Universidad de Valparaíso, Valparaíso, Chile
(2) Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile.
(3) Centro de Estudios Traslacionales en Estrés y Salud Mental (C-ESTRES), Universidad de Valparaíso, Valparaíso, Chile.

Binge eating (BE) is a pathological behavior characterized by the rapid intake of large amounts of food, often accompanied by a perceived loss of control on feeding behavior. This feature may reflect a failure in cognitive mechanisms that regulate feeding. While the lateral hypothalamus (LH) orchestrates motivated feeding behavior, the medial prefrontal cortex (mPFC) exerts top-down control over subcortical structures and is critical for adaptive behavioral regulation. However, whether BE is related to changes in mPFC-LH coordination is not known.

We hypothesize that compulsive feeding will be accompanied by region-specific alterations in neuronal activity patterns, reflecting disrupted modulation of feeding circuits under pathological conditions. To test this issue, here we induced BE behavior by intermittent access to palatable food (PF) in adult female mice, in which simultaneous local field potentials and single-unit recording was performed from the mPFC and LH in every feeding session. Our analyses focus on identifying changes in firing rates and neuronal oscillations associated with bouts of PF or not bout. These findings could shed light on the neurophysiological basis of BE and contribute to a better understanding of the circuit dysfunctions underlying disordered eating in humans.

Funding: This research is supported by scholarship ANID doctorate in Chile(2022), folio 21221792 and regular FODECYT 1231012.

Design of a facial recognition task with ecological validity to be applied to individuals with central vision loss

Taís Dorantes[1], Catalina Espíndola[1], María de los Ángeles Juricic Urzúa[2,3], Iván Plaza Rosales[1,2]

(1) Universidad de Chile, Department of Medical Technology, Faculty of Medicine, Santiago, Chile
(2) Laboratory of Neurosystem, Department of Neurosciences, Faculty of Medicine, Universidad de Chile, Santiago, Chile
(3) Department of Ophthalmology, Faculty of Medicine, Universidad de Chile

Background: Facial recognition is essential for social interaction, and the central visual field plays a critical role in this process. Pathologies such as Age-Related Macular Degeneration (AMD) that damage this area can severely impact quality of life. Training with facial recognition tasks has been shown to improve performance in individuals with central vision loss; however, conventional tasks, such as the Cambridge Face Memory Test (CFMT), lack ecological validity as they omit elements of everyday life (e.g., color, hair, and facial expressions). This limitation could reduce their effectiveness in visual rehabilitation.

Methods: Using a within-subject experimental design, we designed and evaluated a novel facial recognition task with greater ecological validity and compared it with the CFMT in 16 participants with normal vision. We analyzed accuracy, response time, perceived realism, difficulty level, and eye fixation patterns.

Results: Results showed that the Ecological Task produced significantly higher accuracy ($p = 0.0010$) and shorter response times ($p = 0.0034$) than the CFMT. Participants also perceived it as more realistic, easier, more satisfactory, and less stressful. Eye movement analysis revealed fewer and shorter fixations in the Ecological Task while maintaining a similar eye–nose–mouth fixation pattern, though with greater dispersion and fewer central fixations.

Results: These findings suggest that the Ecological Task improves realism and performance in facial recognition compared to conventional tasks. With appropriate difficulty adjustments, it represents a promising training tool for visual rehabilitation in individuals with central vision loss.

Coverage Constraints in Conceptual Property Norms: Comparisons Between Congenitally Blind and Sighted individual reveals differential cognitive processing

Rodrigo Lagos[1], Felipe Toro-Hernández[3], Sergio E. Chaigneau[1], Enrique Canessa[1,2]

(1) Center of Cognitive and Social Neuroscience, School of Psychology, Universidad Adolfo Ibáñez, Santiago, Chile
(2) Facultad de Ingeniería y Ciencias, Universidad Adolfo Ibáñez, Chile
(3) Graduate Program in Neuroscience and Cognition, Federal University of ABC, Sao Paulo, Brazil

Grounded cognition theories hold that conceptual representations are partly formed through interaction, with sensory–motor experiences being crucial for the later neural re-activation (or "simulation") of meaning that supports semantic memory. Comparing congenitally blind and sighted individuals offers a natural setting to assess the role of visual input in the conformation of conceptual structure, especially for concrete concepts with high visual salience (e.g., "dog").

We analyzed the BLIND corpus, a set of conceptual property norms collected from congenitally blind and sighted Italian participants, using the asymptotic Chao2BC estimator to quantify semantic richness for each concept. In this dataset, participants had to name as many items as possible for any given concept. Without coverage filtering, most concepts produced unstable estimates with wide confidence intervals. Applying a ≥0.70 coverage threshold improved precision but reduced the dataset to only two concrete concepts—both showing significant group differences. While consistent with grounded cognition predictions, this outcome reveals a methodological dilemma: increasing reliability through coverage filtering can severely limit representativity, biasing the concepts under study.

These findings have implications for concept theory and for neurophysiological studies that use CPN-derived variables in brain–behavior models. Our results show that grounded cognition models of concepts capture some of the variability in the processing of concrete concepts. However, without high and balanced coverage across concepts, cross-group neurocognitive inferences risk conflating sampling artefacts with genuine neural differences. We recommend CPN designs with sampling strategies that ensure consistently high coverage, enabling robust and generalizable integration of behavioral and neural evidence.

Funding: James S. McDonnell Foundation, A method for studying shared meaning in cultural groups (https://doi.org/10.37717/2022-3930)Fondecyt 1240075.

Coherent eye movements and sound localization during cross-modal active perception

Maria Elena Leon[1], Pedro Maldonado[1,2]

(1) Universidad de Chile, Neuroscience, Medicina, Santiago, Chile
(2) National Center for National Intelligence (CENIA), Santiago, Chile

During active perception, sensory changes occur as a consequence of auto-initiated motor acts. In cross-modal visuo-auditive perception, there is evidence of coordination of perception as early as in the peripheral organs, with the eardrums moving in coordination with eye saccades (Gruters et al., 2018). In this study, we explored the behavioral and electrophysiological correlates of this phenomenon. We designed a cross-modal active perception task in which an image (bird) and a sound (click) appeared in one of the four screen corners against a forest background. Upon an eye movement from central fixation to the target, stimuli either remained together (coherent) or one shifted to another corner (incoherent). Images were presented with three contrast levels. We recorded eye movements and EEG from 20 healthy subjects. Our preliminary analyses of visual behavior show that 42% of first fixations occur on the target, with better performance for higher-contrast stimuli. The fixation duration for coherent stimuli was 336 ms, while it was 323 ms for visual incoherent and 308 ms for auditory incoherent stimuli, respectively. For incoherent trials, 43% of the next saccade ended in the second target. Stimuli presented in the upper corners resulted in better performance than those in the lower corners (63% vs 40%), but were similar for stimuli presented in the left and right positions (49% vs 50%). Our results will shed light on the mechanisms of cross-modal integration during multimodal perceptual tasks.

Funding: The National Center for Artificial Intelligence CENIA, Chile FB210017ANID-Subdirección de Capital Humano/Doctorado Nacional/2022-folio 21221549

Neurochemical changes associated with anxiety-like behavior and relapse after a period of amphetamine withdrawal

Macarena Francisca Gárate Pérez[1,2], Georgina Renard[2]

(1) Universidad de Santiago de Chile, Departamento de Biología, Facultad de Química y Biología, Av. Libertador Bernardo O'Higgins #3363, Estación Central, SANTIAGO, Chile
(2) Universidad de Santiago de Chile, Centro de Investigación Biomédica Aplicada, Ciencias Médicas, Av. Libertador Bernado O'Higgins #3677, Estación Central, SANTIAGO, Chile

Amphetamine (AMPH) withdrawal induces affective symptoms such as anxiety and dysphoria, which increase vulnerability to relapse. In this study, we evaluated how 7- and 14-day withdrawal periods

affect anxiety-like behavior and relapse, along with neurochemical alterations in the nucleus accumbens (NAc), ventral tegmental area (VTA), and amygdala (Amy). Female C57BL/6 mice were subjected to a conditioned place preference (CPP) paradigm, followed by behavioral tests for anxiety (open field and elevated plus maze) and relapse assessment. We quantified tissue levels of dopamine (DA), serotonin (5-HT), norepinephrine (NA), gamma-aminobutyric acid (GABA), and glutamate (GLU) using high-performance liquid chromatography (HPLC) with electrochemical and fluorometric detection.

AMPH (3 mg/kg, i.p.) induced robust CPP ($p < 0.0001$; $n = 9$). The 14-day withdrawal perioddid not significantly alter anxiety-like behavior in the open field ($p = 0.9521$; $n = 8$). However, mice showed a trend toward reduced open-arm exploration in the elevated plus maze ($p = 0.0775$; $n = 8$), suggesting increased avoidance. A subthreshold priming dose of AMPH (1.5 mg/kg, i.p.) reinstated drug-seeking behavior after 14 days ($p = 0.0003$; $n = 6$) and increased total distance traveled ($p = 0.0008$), indicating enhanced sensitivity. In the NAc, GABA levels were significantly reduced ($p = 0.0311$; $n = 8$), and GLU showed a decreasing trend ($p = 0.0728$), while DA/ 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-HT/ 5-hydroxyindoleacetic acid (HIAA) ratios remained unchanged.

These findings suggest that altered GABAergic and glutamatergic transmission in the NAc contributes to relapse vulnerability through mechanisms distinct from monoaminergic pathways in female mice.

Increased feedback-evoked late occipital theta power, global cortical theta coherence, and pupil-indexed arousal during high prediction error trials in an arbitrary associative learning task

Joaquín Valdés Bize[1], Tomás Bosch[1], Roberto García[3], Pedro Maldonado[2], Tomás Ossandón[1]

(1) Neurodynamics of Cognition Laboratory, School of Medicine, Pontificia Universidad Católica de Chile
(2) Laboratorio de Neurosistemas, Facultad de Medicina, Universidad de Chile
(3) Facultad de Psicología, Universidad Diego Portales

The activity of the visual cortex is known to reflect task-dependent factors beyond sensory processing. Yet, its role in performance monitoring remains unclear. We tested whether occipital theta power participates in monitoring during feedback, arguing that it could increase energy efficiency by minimizing prediction errors (PE) early in the cortical hierarchy and/or aligning sensory processing with task goals. Humans performed an arbitrary associative learning task while we recorded EEG theta power over occipital and medial-frontal sensors, as well as pupil diameter (a measure of arousal). Trial-wise PE was modeled using a Rescorla–Wagner framework. Occipital theta was lower on low-PE than high-PE trials 600–1000 ms after feedback, paralleling a medial-frontal effect that occurred earlier. Pupil dilations were larger on high-PE trials. These effects persisted when restricting analyses to the first half of each block and in mixed-effects models that controlled for time-on-task and included random effects for trials and time-on-task. These results suggest that during high-PE trials, the frontal cortex exerts top-down modulation on the occipital cortex. We found that the coherence between fronto-occipital sensors in the theta band did not vary across different trial outcomes. In contrast, global cortical theta coherence was greater on incorrect (high-PE) trials from ~0–500 ms and ~700–1100 ms after feedback. Consequently, the temporal shift from early frontal to later occipital theta during high-PE trials, along with elevated global coherence, suggests that a synchronized cortical state, accompanied by concurrent arousal changes, prepares the occipital cortex to update predictions and associations, thereby supporting learning.

Funding: FONDECYT 1230383

EEG Microstates and the Spatiotemporal Dynamics of Cognitive Processes

Juan Diego Alliende[1], Mario Villena-González[2]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Sociales, Santiago de Chile, Chile
(2) Hospital Clínico Félix Bulnes, Santiago, Chile

We present the EEG microstate technique as a tool to study the spatiotemporal dynamics of brain activity with high temporal resolution. Unlike its traditional use during resting-state, we propose extending its application to low cognitive loaded tasks, exploring its potential to explain various conscious mental processes.

Microstates are quasi-stable topographic configurations of brain electrical activity, lasting between 60 and 120 ms, and occurring in abrupt transitions. They are typically grouped into four canonical classes (A–D), highly replicable across individuals and associated with functional networks such as the default mode network (DMN), dorsal attention network, and visual network. Microstate analysis involves k-means clustering, segmentation based on Global Field Power (GFP) peaks, and temporal backfitting. Commonly assessed metrics include duration, occurrence, coverage, transition probabilities, and Global Explained Variance (GEV).

EEG-fMRI studies have validated the functional relevance of microstates, positioning them as temporal and spatial markers of large-scale brain organization. We will present preliminary results from our laboratory exploring attentional guided somatosensory screening, showing modulations in microstate parameters as a function of subjective experience.

We propose that this technique provides access to the spatiotemporal structure of thought, opening new avenues for investigating consciousness and brain dynamics under conditions beyond resting-state paradigms.

Glial-Derived D-Serine Modulates Oligodendrocyte Lineage Progression Under Inflammatory Conditions

Juan Pablo Espinoza[1,3], Juan José Triviño[2], Ignacio Cisterna[1], Sebastian Alberto Beltran-Castillo[1]

(1) Universidad Bernardo O'Higgins, Centro Integrativo de Biología y Química Aplicada, Ciencias de la Salud, General Gana 1702, Santiago, Chile
(2) Universidad de Chile, Departamento de Química Farmacológica y Tóxicológica, Ciencias Químicas y Farmacéuticas, Olivos 1007, Independencia, Santiago, Chile
(3) Universidad Bernardo O'Higgins, Doctorado en Ciencias Mención

en Materiales Funcionales, Ciencias de la Salud, General Gana 1702, Santiago, Santiago, Chile

D-serine is an endogenous co-agonist of NMDA receptors (NMDARs), synthesized primarily by the enzyme serine racemase (SR) and released by glial cells, including microglia and astrocytes. Inflammatory conditions can upregulate SR expression and promote D-serine release from these cells. Since oligodendrocyte precursor cells (OPCs) and mature oligodendrocytes (OLs) express functional NMDARs, we investigated whether glial-derived D-serine modulates OPC maturation under inflammatory contexts.

Primary OPCs were isolated from neonatal mouse cortices using magnetic-activated cell sorting and cultured in defined conditions. Mixed glial cultures were activated with lipopolysaccharide (LPS) to model inflammatory stimulation, with or without enzymatic D-serine degradation (D-amino acid oxidase, DAAO). Direct D-serine exposure significantly reduced the proportion of $OLIG2^+$ and MBP^+ cells without affecting total cell density, indicating impaired maturation rather than cytotoxicity. Apoptosis analysis revealed that D-serine reduced cell death specifically in mature oligodendrocytes (MBP^+ cells), indicating a stage-specific prosurvival effect. LPS-activated glial cultures showed elevated TNFα release, increased SR expression, and higher extracellular D-serine levels. Conditioned media from these cultures reproduced the inhibitory effects of D-serine on OPC maturation; these effects were prevented when D-serine was degraded with DAAO or when OPCs were treated with the NMDAR antagonist MK-801.

Our findings demonstrate that glial-derived D-serine, acting through NMDARs, can impair OPC progression toward mature OLs under inflammatory conditions, despite enhancing survival of existing mature cells. This dual effect underscores the complex, context-dependent role of D-serine in oligodendrocyte lineage regulation and suggests that targeted modulation of D-serinergic signaling could represent a therapeutic avenue to enhance remyelination in demyelinating diseases.

Funding: FONDECYT de Iniciación 11230857Beca de apoyo Doctorado en Ciencias Mención en Materiales Funcionales, UBO.

Regulation of the inflammatory response as a therapeutic target for congenital hydrocephalus

Fernanda Matamala[1], Luis Muñoz[1], Daniel Muñoz[1], Génesis Aguilar[1], Camila Almonacid[1], Rosa Muñoz[1], Montserrat Guerra[1], Victor Lu[2], Karin Vio[1]

(1) Universidad Austral de Chile, Instituto de Anatomía, Histología y Patología, Facultad de Medicina, Valdivia, Chile
(2) University of Miami, Department of Neurological Surgery, Miami, Florida.

Introduction Congenital hydrocephalus is a brain disorder characterized by the accumulation of cerebrospinal fluid (CSF) into the brain ventricles, and an early neuroinflammatory process affecting cortical development and neural functions. Children born with neurological impairment that it is not solved by CSF shunting. Objective This study aimed to evaluate the effects of an anti-inflammatory treatment on inflammation, memory, and learning in the hydrocephalic brain. Methods Newborn hydrocephalic HTx rats (n=8) were treated with dexamethasone (1 mg/kg) for two consecutive days. On PN7, a subset of animals (n=4) was euthanized, and their brains were analyzed by using histology. Microglia/Macrophages cells were labeled with tomato lectin and antibodies against the Iba1 protein. At PN30, a second group of treated animals (n=4) underwent standardized neurological and behavioral assessments, including the Novel Object Recognition (NOR test). Results and Discussion Early anti-inflammatory treatment significantly reduced the number of activated microglial cells and damage in the cingulum and the rostral migratory stream. Behavioral analyses revealed improvements in some specific neural functions, such as gait, reflexes, and short-term memory following treatment. These findings suggest that dexamethasone treatment regulates microglial function and promotes neural recovery, highlighting its great potential as an adjunct therapy to CSF shunting. Because of dexamethasone exposure activates the TLR4-mediated inflammation pathway, new experiments are advancing by using TAK-42, a TLR-4 antagonist.

Funding: RP-2023-13614

Investigating the effects of social environment and isolation on age-related motor decline using Drosophila melanogaster

Candy Roa Siegfried[1], María Estela Andrés[1], Jorge Campusano[1]

(1) Pontificia Universidad Católica de Chile, Biología celular y molecular, Facultad de Ciencias Biológicas, Santiago, Chile

Social interactions are a fundamental human need comparable to nutrition. Therefore, both social isolation and loneliness have been associated with increased mortality. The WHO has recognized social isolation as a public health concern, creating a commission to promote social connection. Recently, Chile has joined this initiative, taking part in the commission responsible for developing the first Global Report on Social Isolation and Loneliness. Although social isolation can occur at any stage of life, older adults are particularly vulnerable. Thus, studying how social isolation may negatively affect the decline of functions associated with aging is highly relevant. Motor capacity deteriorates with aging, and human studies have suggested that social isolation exacerbates this decline. Nevertheless, these investigations are observational, limiting the ability to draw causal conclusions. In this scenario, animal models become valuable tools. Interestingly, our results show that Drosophila melanogaster socially isolated experience a decline in climbing capacity, a motor behavior that exhibits an age-associated decline in the fly. These results provide us with a model for investigating questions such as: Does the age at which isolation is experienced influence the effects on the motor decline? Is this phenomenon reversible? What neural mechanism underlies these changes? In this study, we propose that the dopaminergic system modulates these changes, and we study its role in transducing housing type and the pattern of motor decline in flies.

Basolateral Amygdala Stimulation Enhances Memory Recovery and Synaptic Plasticity in an Alzheimer's Disease Mouse Model

Daymara Mercerón Martínez[1], Ricardo Ceriani[4], Jaime Maripillán[4], Felipe Conejera[1], Paulina Puebla González[2], Luis Tabilo[1], Elena Mery Bombal[1], Adrián Palacios[5], William Almaguer[3], Alvaro Ardiles Araya[1]

(1) Universidad de Valparaíso, Laboratorio de Sinaptopatías, Facultad de Medicina, Hontaneda 2664, Valparaiso, Chile
(2) Universidad de Valparaiso, Facultad de Biologia, Avenida Gran Bretaña 1091, Valparaiso, Chile
(3) Centro Internacional de Restauración Neurologica, Neurofisiología Experimental, Avenida 25 entre 158 y 162, Atabey, Playa, La Habana, Cuba
(4) Universidad de Valparaiso, Facultad de Farmacia, Valparaíso, Chile
(5) Universidad de Valparaiso, Facultad de Ciencias, Valparaiso, Chile

Background: Alzheimer's disease (AD) is the most common neurodegenerative disorder worldwide, and no effective cure currently exists. The basolateral amygdala (BLA), a brain region involved in emotion, motivation, learning, and memory, plays a key role in promoting neural plasticity. This study investigates whether BLA stimulation can facilitate recovery of spatial memory in 5xFAD mice, a genetic model of AD.

Methods: Twelve to thirteen-month-old 5xFAD mice underwent bilateral stereotactic implantation of stimulation electrodes in the BLA. Fifteen minutes after behavioral training, the BLA was stimulated with 3 trains of 15 pulses at 200 Hz. A week later, mice were trained in the Morris Water Maze (MWM) for five days, followed by BLA stimulation 15 minutes after each session. To test for general memory recovery, two additional behavioral tasks were used: the Novel Object Recognition Test (NORT) and the Place Recognition Test (PRT). Finally, long-term potentiation (LTP), a synaptic model of learning and memory that is impaired in 5xFAD mice, was evaluated after MWM plus BLA stimulation.

Results: MWM training combined with post-session BLA stimulation for four days restored memory in 5xFAD mice. Importantly, performance also improved in NORT and PRT, suggesting a general recovery of memory function. Additionally, LTP was enhanced, particularly in its maintenance phase, which typically declines rapidly in 5xFAD mice.

Conclusions: BLA stimulation combined with behavioral training enhances neural plasticity and induces recovery of memory functions in 5xFAD mice. These findings suggest a potential therapeutic strategy for memory loss in Alzheimer's disease.

Funding: Fondecyt Postdoctorado 3230293

6-MeOisoDMT restores hippocampal synaptic plasticity deficits in a murine model of depression

Catalina Rozas[1], Felipe Godoy[1], José Rojas-Burgos[2], Bruce K. Cassels[2], Bernardo Morales Muñoz[1], Carlos Rozas[1]

(1) University of Santiago de Chile, Department of Biology, Faculty of Chemistry and Biology, AV.Libertador Bernardo O'Higgins 3363, Santiago, Chile
(2) University of Chile, Department of Chemistry, Faculty of Sciences, Las Palmeras 3425, Santiago, Chile

Most symptoms that characterize major depressive disorder (MDD) converge on cognition, memory and synaptic impairment. The use of psychedelic compounds has gained attention in the past years, especially in patients refractory to traditional antidepressant treatments, because it can overcome deficits in synaptic plasticity and dendritic spine growth. Nevertheless, the high comorbidity of MDD with other neurological disorders, such as psychotic outbreak from exposure to hallucinogenic compounds, has hindered its clinical applications. An alternative is the use of derivatives of N,N-dimethyltryptamine (DMT) with minimal hallucinogenic/like responses in mice. We studied the effects of the non-hallucinogenic 6-Methoxy-N,N-dimethylisotryptamine in the Learned Helplessness (LH) murine depression model. The LH model is generated by foot shock exposure for two consecutive days (360 pulses, 0.3mA, duration 1-3 s, interval 1-15 s), inducing behavioral despair measured as immobility at the third day in the Forced Swim test (Control=73.9 ± 8.3 s, n=14; LH=156.8 ± 6.8 s, n=19; Mann-Whitney test P<0.0001). Regarding hippocampal neurotransmission, we found that LH mice present smaller field potentials, normal paired pulses facilitation and reduced long-term potentiation (LTP) of CA3-CA1 synapses compared to control animals (Control=153.7± 3.9%,n=9; LH=121.4± 2.4%,n=15; Mann-Whitney test, P <0.0001). Acute exposure to 6-MeOisoDMT (10μM) recovers the hippocampal LTP of LH mice (LH=150.5±3.9%, Kruskal-Wallis test, P > 0.999) but does not enhance the LTP in control animals (control+6-MeOisoDMT= 152.6±2.6%, Kruskal-Wallis test, P>0.999). In conclusion, exposure to 6-MeOisoDMT enhances hippocampal synaptic plasticity and restores the impairment in LH mice.

Funding: ANID 212208073 to F.G., FONDECYT1221682 to B.K.C., FONDECYT 1161524 to B.M., DICYT-USACH 021843MM to B.M.,FONDECYT 11140430 to C.R., DICYT-USACH 0211843RS to C.R.

The emerging significance of lipids in plasma-derived extracellular vesicles to improve the diagnosis of Monopolar Depression and Bipolar disorder

Bárbara Maturana[1,2], Maxs Méndez-Ruette[1,2], Ingrid Contardo[1], Ariel Caviedes[1], Gino Nardocci[1,2], Thilo Kaehne[4], Miguel Prieto[2,3], Mauricio Mastrogiovanni[5], Homero Rubbo[5], Alejandro Luarte[1,2], Úrsula Wyneken[1,2]

(1) Facultad de Medicina, Universidad de los Andes, Chile.
(2) IMPACT, Center of Interventional Medicine for Precision and Advanced Cellular Therapy, Santiago, Chile.
(3) Clínica Universidad de Los Andes, Santiago, Chile.
(4) Center for Mass Spectrometry, Otto-von-Guericke University, Magdeburg, Germany.
(5) Universidad de la República, CENBIO, Medicina, Montevideo, Uruguay

Monopolar Depression (MD) and Bipolar Disorder (BD) are two prevalent mood disorders, affecting approximately 9% and 3% of the population, respectively. While depressive episodes are common to both conditions, BD includes alternating manic phases. Given that extracellular vesicles (EVs) mirror the pathological state of cells, including brain cells, and are known to reach the blood stream, we developed a diagnostic approach using plasma-derived EVs from ten patients per group (MD, BD in depressive phase, BD in euthymic phase and healthy controls) recruited at the Clinica Universidad de Los Andes. Small EVs (sEVs) were enriched from plasma using Total Exosome Isolation Kit (Invitrogen) and analyzed via Western blotting, Nanoparticle Tracking Analysis (NTA), Raman spectroscopy, proteomics and lipidomics. Canonic sEVs markers, such as CD-63 and flotillin-1 were detected. NTA showed no

significant differences in sEVs concentration between groups. Raman spectroscopy revealed spectral differences at 720, 876, and 1641 cm^{-1}, corresponding to phosphocholine, choline, and amide I, indicating compositional changes in EVs protein and lipid cargo. Proteomic profiling identified 1233 proteins, with differential enrichment in lipid metabolism-associated pathways. Western blot analysis revealed altered expression of three enzymes involved in sphingolipid metabolism—Neutral Sphingomyelinase 2, Acid Sphingomyelinase, and Neuraminidase 2—suggesting their potential as biomarkers to discriminate MD from BD. Moreover, quantitative lipidomic profiling identified sphingolipids such as ceramide, sphingomyelin and phosphocholine species with 100% predictive capacity. Our findings reveal an unprecedented role of ceramides and sphingomyelins in sEVs as a reliable diagnostic approach to discriminate between MD and BD in its depressive phase.

Funding: IMPACT #FB210024, Fondecyt 1200693, Fondef ID19I10116

Non-rem sleep characterization of patients with long covid and brain fog

Teresa Córdova Bustos[1,2], Cristóbal Vargas[1,2], Danay Espinoza[1], Mirliana Ramirez[6], Mario Díaz[7], Alonso Quijada[3], Roberto Arellano[5], Mercedes López[4], Adrián Ocampo[1]

(1) Universidad de Chile, Laboratorio de Sueño y Cronobiología, Facultad de Medicina, Independencia 1027, Santiago, Chile
(2) Universidad de Chile, Departamento de Tecnología Médica, Facultad de Medicina, Independencia 1027, Santiago, Chile
(3) Hospital Clínico de la Universidad de Chile, Neurología, Carlos LorcaTobar 999, Santiago, Chile
(4) Universidad de Chile, Programa de Inmunología, Facultad de Medicina, Independencia 1027, Santiago, Chile
(5) Hospital del Salvador, Neurología, Av. Salvador 364, Santiago, Chile
(6) Universidad de Chile, Departamento de Enfermería, Facultad de Medicina, Independencia 1027, Santiago, Chile
(7) Universidad de Santiago de Chile, Escuela de Medicina, Facultad de Medicina, Av. Libertador Bernardo O'Higgins 3363, Santiago, Chile

Long COVID syndrome includes "brain fog," characterized by persistent cognitive impairment. Given the crucial role of sleep in cognitive function, sleep alterations could contribute to this symptom. Although there are reports of brain changes in patients with post-COVID brain fog, studies employing polysomnography in this population remain scarce. This study evaluated the integrity of NREM sleep in patients with persistent COVID and brain fog compared to healthy controls. Seven patients with Long COVID (6 with brain fog) and 6 healthy controls participated, assessed through clinical interviews, sleep questionnaires, and polysomnography. The brain fog group exhibited increased sleepiness, insomnia, and poorer sleep quality. They showed a higher proportion of N3 sleep, as well as alterations in sleep efficiency, arousal index, and sleep-stage distribution compared to clinical references. In sleep microstructure, they demonstrated lower delta power during N3, increased theta activity during N2 and N3, and higher alpha and sigma activity during N1. Analysis of the coefficient of variation of the envelope revealed differences in the distribution and dynamics of NREM sleep. These findings suggest reduced NREM sleep integrity in patients with post-COVID brain fog.

Funding: This study was supported by Fundación Puelma and FONDECYT project 1231901.

Effect of photobiomodulation and semaglutide treatment in mice with a diabetic retinopathy model

Ricardo Cespedes Jara[1], Oliver Schmachtenberg[2]
(1) Universidad de Valparaíso, Doctorado en Ciencia, mención Neurociencia, Facultad de Ciencia, Valparaíso, Valparaíso
(2) Universidad de Valparaíso, Deparatamento de Biologia, Facultad de Ciencias, Valparaíso, Valparíso

Type 2 diabetes mellitus affects approximately 10% of the global population, and 20% of these patients already present diabetic retinopathy (DR) at the time of diagnosis. DR is a progressive microangiopathy that triggers oxidative stress, neuronal apoptosis, and ultimately leads to vision loss. Current treatments for DR are often invasive and fail to reverse the underlying pathology, highlighting the urgent need for more effective and less invasive therapeutic options.
Photobiomodulation (PBM) has shown promising potential in reducing inflammation, oxidative stress, and neuronal apoptosis in various retinal diseases. However, its therapeutic efficacy in diabetic retinopathy—particularly in comparison with established pharmacological treatments—remains relatively underexplored.

The aim of this study was to compare the effects of PBM alone and in combination with semaglutide on the eyes of mice with a type 2 diabetes model (db/db). Multiple microscopy-based analyses were performed, including toluidine blue staining, mitochondrial superoxide detection using MitoSOX, and immunofluorescence to assess NF-kB, VEGF, and GFAP expression. Additionally, visual function was evaluated using an adapted water maze test and pattern ERG recordings.

Results showed that the combined PBM and semaglutide treatment improved visual function and reduced NF-kB expression. These findings suggest that the combination therapy may help delay hyperglycemia-induced damage in the db/db mouse model.

When the Ground Shifts: Biomechanical Alterations in Extracellular Matrix Derived from Schizophrenia Astrocytes

Sebastián Arizábalos Campos[1], Dan Perez[1], Fabian Rivera[1], Verónica Palma[1]
(1) Universidad de Chile, Biología, Ciencias, Las Palmeras 3370, Santiago, Chile

Schizophrenia (SZ) is a neurodevelopmental disorder driven by genetic and environmental interactions, leading to cellular, molecular, and functional alterations in multiple central nervous system cell types. Evidence, including our findings on the heightened inflammatory profile of SZ hiPSC-derived astrocytes, suggests that astrocyte dysfunction contributes to disease pathophysiology not only through aberrant signaling but also by altering the composition and organization of the extracellular matrix (ECM). ECM is increasingly recognized as a dynamic regulator of cell fate and function, whose biomechanical properties (BP) may

critically influence neural development and disease progression.

Transcriptomic analyses and enzymatic assays of postmortem SZ brain tissue reveal imbalances in ECM component synthesis and degradation. Concordantly, in vitro studies using hiPSC-derived astrocytes (the main neural source of ECM deposition) indicate that such alterations arise early in development.

In this work, we investigated the BP of ECM from SZ and healthy control (HC) hiPSC-astrocyte cultures at two maturation stages (5 and 9 weeks). Using a novel methodology, we isolated ECM from monolayers, characterized glycosaminoglycan content by histological staining, and analyzed topographic features via Atomic Force Microscopy, including surface roughness, peak–valley patterns, and ECM symmetry.

Our results reveal distinct BP in ECM from SZ astrocytes compared to HC, with additional stage-specific differences within each group. These findings suggest that SZ-associated ECM alterations are dynamic and evolve with astrocyte maturation, influencing cellular, molecular, and functional phenotypes over neurodevelopment. Integrating BP with our previous insights into astrocyte inflammation offers a novel perspective on how the cellular microenvironment shape SZ onset and progression.

Funding: Nº Fondecyt 1221522 (VP Lab).

Even flies need therapy: Fluoxetine reverts depression-like behaviors induced by chronic stress in Drosophila

Simón Guerra-Ayala[1], Paula Amado-Hinojosa[1], Jorge M Campusano[1]

(1) Pontificia Universidad Católica de Chile, Laboratorio de Neurogenética de la Conducta, Facultad de Ciencias Biológicas, Av. Libertador Bernardo O'Higgins 340, Santiago, Chile

Depression, a highly prevalent neuropsychiatric disorder, is expected to be the leading cause of morbidity by 2030. The limitations of current treatments for this condition support further studies on how depressive behavior is established and maintained, in the search for possible new therapies. It has been proposed that chronic stress can lead to a depressive-like state in animals. Drosophila melanogaster is an important animal model in understanding the cellular, molecular, and circuital mechanisms underlying several brain conditions, including depression.

We are assessing the consequences of exposing flies to a previously described chronic-unpredictable stress treatment (CST). We study behavioral despair in these flies by using the forced swim test (FST). Our results indicate that CST induces behavioral despair in male and female flies, a behavior that can be prevented by feeding flies fluoxetine (FLX). Remarkably, locomotor parameters remain unchanged. These results demonstrate the predictive validity of our protocol. We are carrying out experiments to demonstrate that FLX can also prevent the anhedonia-like behavior detected in CST-exposed flies. Finally, we are evaluating the progression of the depressive-like features after CST treatment, to characterize the dynamics of temporal changes in this depression model.
Our results suggest that CST induces a depressive-like state in Drosophila. The study of the time-induced changes in this depression model could provide new insights about the etiology of the condition and novel therapeutic approaches.

Funding: Funded by Fondecyt 1231556 (JMC). ANID PhD fellowships No. 21221773 and 21240831 support PAH and SGA.

SARS-CoV-2 spike protein S1 increases the activity of astroglial hemichannels: potential implications for cellular dysfunction and NeuroCOVID

Juan Carlos Prieto Villalobos[1], Arantza Farías-Pastén[1], Sergio A. Vergara[1], Eliseo A. Eugenín[2], Juan A. Orellana[1]

(1) Pontificia Universidad Católica de Chile, Departamento de Neurología, Escuela de Medicina and Centro Interdisciplinario de Neurociencias, Facultad de Medicina, Santiago, Chile
(2) The University of Texas Medical Branch (UTMB), Department of Neurobiology, Galveston, Texas, United States of America

NeuroCOVID refers to neurological symptoms observed in individuals with COVID-19 and Long-COVID, including headaches, cognitive decline, among others. However, it remains uncertain whether these symptoms arise from SARS-CoV-2 virus itself, associated systemic inflammation, or viral proteins (e.g., spike protein S1 [spike S1]). Relevantly, the persistent activation of hemichannels composed of connexin-43 (Cx43) or pannexin-1 (Panx1) plays a crucial role in amplifying virus-induced cellular damage in astrocytes. Moreover, during infection, spike S1 is cleaved from SARS-CoV-2 and released into the interstitium. From there, it can cross the blood-brain barrier, directly affecting brain cells. Whether spike S1 affects hemichannel activity in astrocytes and how this modulation impacts astroglial function remains unanswered. In this context, we stimulated primary human and mouse astrocyte cultures or acute brain slices of mice with spike S1 (10-1000pM) for 1-72 h or 1-3 h, respectively. Using dye uptake techniques combined with epifluorescence and confocal microscopy, we found that spike S1 induced a time-and concentration-dependent increase in Cx43 and Panx1 hemichannel activity in astrocytes. These responses were sensitive to the inhibition of the metabotropic glutamate receptor, glutamatergic ionotropic NMDA receptor, and cyclooxygenase-2, suggesting their involvement in spike S1-induced astroglial hemichannel activation. Notably, spike S1-induced hemichannel opening resulted in increased nitric oxide production, a high release of ATP, exacerbated K^+-induced $[Ca^{2+}]_i$ dynamics, and reduced cell viability, as measured by DAF-FM, luciferin/luciferase, and FURA-2 fluorescent/bioluminescent assays and TUNEL/Ethidium homodimer, respectively. We hypothesize that spike S1-induced opening of astroglial Cx43 and Panx1 hemichannels could contribute to NeuroCOVID pathogenesis and progression.

Funding: ANID-Subdirección de Capital Humano/Doctorado Nacional/2022-21221569 and FONDECYT-1250847

Heart Rate in a Fragile X Syndrome (FXS) Mouse Model: Assessment in Conscious Behaving and Anesthetized Mice.

Daniel Zepeda[1], Julio Alcayaga[1], Alexia Núñez-Parra[1]

(1) Universidad de Chile, Biology, Cell Physiology and Neurobiology Laboratory, Las Palmeras 3425, Santiago, Chile

Fragile X Syndrome (FXS), the leading hereditary monogenic cause of autism spectrum disorder (ASD) and intellectual disability, caused by silencing of the Fmr1 gene encoding an mRNA-regulating protein, affects nervous system development and function. FXS individuals exhibit physical and cognitive alterations, including hyperactivity, hyperreactivity to stimuli, and elevated heart rate (HR). The vagus nerve, the main heart parasympathetic controller, efferently reduces HR, and afferently activates several central neuromodulatory regions. Although humans with FXS show reduced vagus nerve activity, there is no characterization of HR in Fmr1 KO mice, the most widely used FXS animal model. We assessed HR in wild-type (WT) and Fmr1 KO mice during anesthesia and awake, free-roaming conditions, from electrocardiograms recorded with subdermal surgically implanted electrodes. Mice were first recorded during surgical anesthesia, and in two to three awake periods, over two weeks after surgery. Our results show that while Fmr1 KO and WT mice exhibit similar HR under ketamine/xylazine (293 ± 9 vs 278 ± 9 BPM) and chloralose/urethane (591 ± 17 vs 625 ± 45) anesthesia, HR was elevated in Fmr1 KO (712 ± 12 BPM) compared to WT (661 ± 20 BPM) mice in behaving animals, replicating human physiological findings. This first assessment of HR in non-human FXS models allows its application in novelty and social anxiety tests to evaluate stress and excitability in the FXS model. It also opens up possibilities to study the effects of vagus nerve stimulation on social stress, a technique gaining ground as a therapy for ASD symptoms.

Exploring the UPR pathway effects in synaptic activity of cortical neurons: Are the inhibitory component altered in pathological conditions?

Valentina De La Fuente Vega[1], Santiago Quintana Herrera[1], Paul Soto Ortega[1], David Flaig Lobos[1], Carla Torres Fuentes[1], Tamara Cáceres Palma[1], Ninoschka Troncoso Rivas[1], Alejandra Fuentes Garrido[1], Human Rezaei[2], Carola Muñoz-Montesino[1], Gustavo Moraga-Cid[1]

(1) Unversidad de Concepción, Departamento de Fisiología, Facultad de Ciencias Biológicas, Barrio Universitario, Concepción, Chile
(2) INRAE, MAP2, VRIM, Jouy en Josas, Francia

The cellular prion protein (PrP^{C}) can misfold into its pathogenic form (PrP^{Sc}), leading to transmissible spongiform encephalopathies (TSEs). This process induces endoplasmic reticulum (ER) stress and activates the Unfolded Protein Response (UPR). The UPR pathway has three main branches aimed at restoring proteostasis. One branch involves PERK-mediated phosphorylation of eIF2α, which reduces global protein translation. UPR inhibition has been shown to decrease neurotoxicity without affecting PrP^{Sc} levels, while UPR activation reduces PrP^{C} levels, potentially limiting PrP^{Sc} formation.

Despite de relevance of UPR in prion pathology, its effect over excitatory and inhibitory synaptic activity either in normal or prion-infected conditions, remains unexplored.
This study evaluated the effects of UPR activation on postsynaptic excitatory and inhibitory activity in cortical neurons from E15 mice cultivated in vitro for 12 days were treated with increasing concentrations of tunicamycin (1 to 2 ug/ml) to activate the UPR system. The impact of tunicamycin on the spontaneous postsynaptic activity was evaluated by whole-cell electrophysiological recordings. Moreover, PrP and phosphorylated eIF2α-P levels were evaluated by Western blot and immunofluorescence analysis.
Ours experimental data showed that tunicamycin (2ug) induced the phosphorylation of eIF2α. Electrophysiological recordings revealed changes in the mean amplitude as well as in the frequency of inhibitory postsynaptic currents. These findings indicate that UPR activation enhances inhibitory synaptic transmission in cortical neurons and suggest a potential modulatory role of UPR in prion-related synaptic dysfunction.

Funding: Fondecyt 1251488

Early synaptic plasticity impairment in D1R+ accumbal neurons associated with CP-AMPAR accumulation in an Alzheimer's disease mouse model.

Nicolas Riffo Lepe[1], Juliana Gonzalez-Sanmiguel[1], Lorena Armijo-Weingart[2], Paulina Saavedra-Sieyes[1], Helena Zambrano[1], Ailin Riquelme[1], Loreto SanMartin[2], Isaías Meza[1], Luis Aguayo[1,2]

(1) Universidad de Concepción, Departamento de Fisiología, Facultad de Ciencias Biológicas, Concepción, Chile
(2) Universidad de Concepción, Programa de Neurociencia, Psiquiatría y Salud Mental (NEPSAM), Facultad de Medicina, Concepción, Chile

Alzheimer's disease (AD) is traditionally characterized by progressive cognitive impairment; however, early non-cognitive symptoms such as apathy and compulsive behavior suggest that dysfunction in reward-related circuits may precede memory decline. The nucleus accumbens (nAc), a key mesolimbic hub, has emerged as an early target of AD pathology, although the underlying synaptic mechanisms remain poorly understood. To address this, we used APPswe/PS1E9d (2xTg) mice crossed with Drd1a-TdTomato mice to label D1 receptor-expressing medium spiny neurons (D1+ MSNs). At 6 months, intracellular amyloid-beta (Aβ) accumulation was observed in both D1+ and D1− MSNs without extracellular plaques. Whole-cell voltage-clamp recordings revealed impaired induction of long-term depression (LTD) specifically in D1+ MSNs of 2xTg mice, following high-frequency stimulation or chemical LTD induced by DHPG, an mGluR1/5 agonist. While LTD normally promotes removal of calcium-permeable AMPA receptors (CP-AMPARs), this process failed in 2xTg D1+ MSNs, associated with increased rectification index and NASPM sensitivity, indicating impaired CP-AMPAR clearance. GCaMP6s imaging confirmed elevated AMPAR-mediated calcium responses in 2xTg mice. Protein analysis of nAc tissue revealed upregulation of postsynaptic markers, including PSD95, GluA1, and GluA2, while presynaptic markers and paired-pulse ratio remained unchanged, suggesting selective postsynaptic remodeling. Although anxiety-like behavior and social interaction were unaffected, 2xTg mice exhibited increased chocolate consumption in a conditioned place preference task. Additionally, fiber photometry using DLight1.1 revealed reduced dopamine release in the nAc of 2xTg mice.

These findings reveal early synaptic and neuromodulatory impairments in D1+ MSNs that may underlie non-cognitive dysfunction preceding memory decline in AD.

Funding: Funding: NIH R01AA025718, Fondecyt-1221080, PhD ANID fellowship-21202521

Predictive Models of 5-HT1A Receptor Ligands Using Computational Chemistry and Machine Learning

Francesca Cáceres San Martín[1], Andrés Halabi Díaz[2,3,4], Elizabeth Rincón Bedoya[1], Eduardo Chamorro Jiménez[5]

(1) Universidad Austral de Chile, Instituto de Ciencias Químicas, Facultad de Ciencias, Independencia 631, Valdivia, Chile
(2) Universidad Andrés Bello, Departamento de Ciencias Químicas, Facultad de Ciencias, Avenida República 275, Santiago, Chile
(3) Good Research and Science (GRS), Departamento de Investigación y Desarrollo, Avenida Ramón Picarte 780, Valdivia, Chile
(4) CatchPredict SpA, Departamento de I+D+i, Avenida Ramón Picarte 780, Valdivia, Chile
(5) Universidad San Sebastián, Facultad de Ingeniería, Avenida del Cóndor 720, Santiago, Chile

Serotonin dysregulation in the central nervous system is closely linked to anxiety and mood disorders. While current pharmacological treatments are available, issues such as side effects, treatment-resistance patients, and limited efficacy underscore the need for new therapeutic compounds. In this context, computational strategies that support drug design are increasingly valuable.

This study presents predictive models to estimate the activity of 5-HT_{1A} receptor ligands using a combination of computational chemistry and machine learning (ML) techniques. A dataset of 94 molecules was classified as active or inactive based on experimental Ki values. Electronic descriptors derived from Conceptual Density Functional Theory (CDFT) were calculated for both neutral and protonated forms, in vacuum and aqueous environments, to simulate biological conditions.

Quantitative Structure-Activity Relationship (QSAR), Quantitative Structure-Property Relationship (QSPR), and ML algorithms were applied to build classification models. Most models achieved recall and F1-score values above 70%, with Kappa statistics generally exceeding 0.3. Descriptors from protonated molecules in aqueous solvent emerged as the most informative, with chemical hardness consistently appearing as the root node in decision trees, highlighting its role in initial classification.

These findings suggest that incorporating the protonation state and aqueous solvent effects significantly enhances the predictive power of QSAR models. Future work will explore additional CDFT-derived descriptors and regression-based approaches to better prioritize compounds by binding affinity, contributing to the development of more effective treatments.

Characterization of Brain Age in Healthy Adults and Patients with Neurodegenerative Diseases through the Analysis of Resting-State Brain Networks.

Andrea Fernández Jerez[1], Lien Rodríguez[1], Agustín Ibáñez[2], Pavel Prado[3], Mónica Otero[1,4]

(1) Universidad San Sebastián, Facultad de Ingeniería, Concepción, Chile
(2) Universidad Adolfo Ibañez, Instituto BrainLat, Santiago, Chile
(3) Universidad San Sebastián, Facultad de Ciencias de la Rehabilitación y Calidad de Vida, Santiago, Chile
(4) Universidad San Sebastián, Fundación Ciencia y Vida, Santiago, Chile

Brain age is an estimation of the brain's functional status that may differ from chronological age and reflect either accelerated aging or early alterations occurring before the onset of clinical symptoms. Based on characteristic patterns of brain activity, brain age has been proposed as a potential biomarker for the risk of developing neurodegenerative conditions such as Alzheimer's disease (AD) or frontotemporal dementia (FTD). Resting-state brain networks, inferred from electroencephalography (EEG) recordings, have been suggested as representations of the brain's spontaneous functional organization, and may serve as a framework to characterize alterations related to aging processes or pathological changes. In this study, resting-state EEG signals from 1,644 healthy controls and 1,134 patients with neurodegenerative diseases, collected across 10 different countries were analyzed. After estimating the cortical sources of the recorded EEG activity, brain regions were grouped according to their membership in predefined resting-state networks. Subsequently, both linear and nonlinear connectivity metrics were computed across temporal and spectral domains. For each functional network and frequency band, these metrics were employed as features in machine learning models, specifically using the XGBoost algorithm, to estimate individual brain age. The findings demonstrate that each functional network displays a distinct aging trajectory, and that individuals with AD or FTD show specific deviations from typical patterns. This non-invasive analytical approach offers a promising avenue for early detection, monitoring, and potential intervention in neurodegenerative disorders.

Funding: Fondecyt Iniciación 11241484, Basal FB21008, Exploración 13240042.Vicerrectoría de Investigación y Doctorados -proyecto "USS-FIN-25-PASD-04".

Selective Frequency Control of the Whole-Brain Kuramoto Network

Felipe Torres[1], Alejandro Weinstein[2], Mónica Otero[3,4], Caroline Lea-Carnall[5], Pamela Guevara[6], Wael El-Deredy[7]

(1) Universidad Católica del Maule, Departamento de Computación e Industrias, Talca, Chile
(2) Universidad Técnica Federico Santa María, Department of Electronic Engineering, Valparaíso, Chile
(3) Universidad San Sebastián, Facultad de Ingeniería, Arquitectura y Diseño, Santiago, Chile

(4) Universidad de San Sebastián, Fundación Ciencia y Vida, Santiago, Chile
(5) University of Manchester, Manchester Academic Health Science Center, Manchester, United Kingdom
(6) Universidad de Concepción, Department of Electrical Engineering, Concepción, Chile
(7) Universidad de Valparaíso, Brain Dynamics Laboratory, Valparaíso, Chile

Several brain disorders, such as frontal dementia, mild cognitive impairment, and obsessive-compulsive disorder, have a relation to changes in the dynamics of the brain activity in comparison to healthy control subjects. The rhythmic and the aperiodic components of the MEG/EEG spectrum suffer alterations by changes in the large-scale structure and changes in the excitatory/inhibitory balance. Although rhythmic electrical or sensory stimulation does not directly recover the structure or neurotransmitter concentration, the entrainment of brain activity at the stimulation frequency has been proposed as a neurorehabilitation mechanism.

Here, we apply control theory to a whole-brain Kuramoto model, which is an oscillator network, to find the adequate frequency and position of stimulation to achieve the entrainment of selective functional networks. It is expected that if the entrainment frequency matches the prepreferred functional frequency, there would be rehabilitation of the cognitive function related to the network. We show analytic results for the analytical quasi-synchrony regime of network activity, and numerical results for the metastable regimes, suggested as the dynamic regime of the awake brain. The selectivity of the functional sub-network is still challenging when applying rhythmic stimuli in the metastable regime of brain dynamics.

Financing: This work was supported by ANID: Fondecyt Postdoctorado 3230682, Exploración 13240064, Fondecyt Iniciación 11241484, Fondecyt Regular 1241695, 1221665, 1231132.

Frequency-Dependent Propagation of Neural Entrainment in a Large-Scale Brain Model

Elida Poo[1], Felipe Torres[2], Cristobal Mendoza[1], Caroline Lea-Carnall[3,4], Alejandro Weinstein[5], Pamela Guevara[1], Pavel Prado[6], Joana Cabral[7], Wael El-Deredy[8], Mónica Otero[9,10]

(1) Universidad de Concepción, Department of Electrical Engineering, Faculty of Engineering, Concepción, Chile
(2) Universidad Católica del Maule, Departamento de Computación e Industrias, Facultad de Ciencias de la Ingeniería, Talca, Chile
(3) University of Manchester, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester, United Kingdom
(4) University of Manchester, Manchester Academic Health Science Center, Manchester, United Kingdom
(5) Universidad Técnica Federico Santa María, Department of Electronic Engineering, Valparaíso, Chile
(6) Universidad San Sebastián, Escuela de Fonoaudiología, Santiago de Chile, Chile
(7) Minho University, Life and Health Sciences Research Institute, Braga, Portugal
(8) Universidad de Valparaíso, Brain Dynamics Lab, Interdisciplinary Center of Biomedical and Engineering Research for Health, Valparaíso, Chile
(9) Universidad San Sebastián, Facultad de Ingeniería, Universidad San Sebastián, Chile
(10) Fundación Ciencia y Vida, Santiago de Chile, Chile

Non-invasive neurostimulation techniques such as tACS and rTMrTMS hold promise for modulating brain dynamics in neurological and psychiatric disorders. However, the mechanisms by which rhythmic inputs influence distant network regions remain poorly understood. While previous studies have shown that stimulation frequency and target location shape local entrainment, how these parameters modulate propagation beyond direct structural connections is still unclear.

In this study, we used a large-scale model of coupled forced Kuramoto oscillators to examine frequency- and site-dependent propagation of neural entrainment. Simulations were based on human connectome-derived structural topology, with periodic stimulation applied to individual nodes across multiple frequencies. Entrainment was assessed through increases in spectral amplitude and phase-locking to the external input.

Our results show that entrainment can extend to regions not structurally connected to the stimulation site, especially at lower frequencies such as 13 Hz. High-degree hubs like the precuneus, a central node of the default mode network, effectively broadcast stimulation across the network via indirect pathways. In contrast, higher frequencies such as 43 Hz produced more spatially restricted effects.

These findings indicate that entrainment propagates along functional pathways determined by both network topology and stimulation frequency. This insight may help guide the development of frequency-targeted interventions to restore impaired brain dynamics in conditions with known frequency-dependent connectivity disruptions. Future work will incorporate individual connectomes to enhance subject-specific predictions. To the best of our knowledge, this framework represents a significant step forward in computational neuromodulation, enabling non-invasive stimulation strategies beyond the cortex.

Funding: This research was supported by ANID, Chile:FONDECYTs Iniciación 11241484 (MO), Exploración 13240042 (MO), 13240064 (WED); and ANID/Basal/FB210008 (MO).

Altered Short- and Long-Term Entrainment Dynamics in Schizophrenia: A Study of Gamma-Band ASSRs

Leonardo Zúñiga[1], Andre Gómez[2], María Francisca Alonso-Sánchez[2], Pavel Prado[3], Mónica Otero[4]

(1) Universidad San Sebastián, Doctorado en Biología Computacional, Facultad de Ingeniería, Santiago, Chile
(2) Universidad de Valparaíso, Centro de Investigación del Desarrollo en Cognición y Lenguaje, Valparaíso, Chile

(3) Universidad San Sebastián, Facultad de Ciencias de la Rehabilitación y Calidad de Vida, Santiago, Chile
(4) Universidad San Sebastián, Facultad de Ingeniería, Santiago, Chile

Neural entrainment is the synchronization of neuronal activity with external rhythmic stimuli and provides a way to study short- and long-term brain dynamics. These dynamics reflect the brain's ability to adapt and reorganize in response to stimulation, and these processes can be altered in disorders such as schizophrenia. A key
manifestation of this adaptive capacity is habituation, defined as the progressive reduction of neuronal responses to repeated stimuli, enabling the prediction and filtering of redundant sensory information.

In this study, electroencephalography (EEG) was recorded from 20 healthy participants and 20 patients with schizophrenia during the presentation of 40 Hz amplitude-modulated auditory stimuli, eliciting Auditory Steady-State Responses (ASSRs). EEG signals were segmented into consecutive epochs, and spectral amplitude within the gamma band was computed as an index of neuronal responsiveness.

Healthy controls demonstrated a clear habituation pattern, with gamma-band potential amplitudes progressively decreasing as stimuli were repeated, reflecting normal adaptive mechanisms. Conversely, patients with schizophrenia exhibited reduced or absent amplitude declines, indicating disruptions in the brain's predictive dynamics. Additionally, two auditory processing stages were examined: the initial integration of the stimulus until the ASSR is stablished and the persistence of the response after stimulus offset. Both stages were found to be prolonged in patients, suggesting impairments in the proper modulation of neural activity when processing repetitive stimulation.

These findings reveal an altered pattern of neuronal adaptation in schizophrenia, offering insights into the mechanisms of synchronization and prediction disrupted in this pathology.

Funding: Fondecyt Iniciación 11241484, Basal FB21008, Exploración 13240042, VRID Scholarship, Universidad San Sebastián (Folio No. 10267285).

Systems-Level EEG Modelling Reveals Thalamocortical Mechanisms Underlying Consciousness and Sensory Awareness

Vicente Medel[1], Eli J. Muller[2,5], Brandon R. Munn[2], Cameron Casey[4], Robert D. Sanders[3], James M. Shine[2,5]

(1) Universidad Adolfo Ibáñez, Latin American Brain Health Institute, Facultad de Psicología, Diagonal Las Torres 2640, Santiago, Chile
(2) The University of Sydney, Brain and Mind Center, 94 Mallett St, New South Wales, Australia
(3) The University of Sydney, Anaesthetics & Institute of Academic Surgery, Royal Prince Alfred Hospital, 50 Missenden Rd, New South Wales, Australia
(4) University of Wisconsin-Madison, Department of Anesthesiology, 600 Highland Ave B6/319, Madison, USA
(5) The University of Sydney, Centre for Complex System, New South Wales, Australia

While consciousness never fades during wakefulness, there is a paradoxical coexistence of consciousness during dreaming states. It's also possible for sensory awareness to be either present or absent when awakened from seemingly identical states of sedation and anaesthesia. Traditionally, these states have been characterised in terms of their electroencephalographic neural correlates, however, without clear underlying neurobiological mechanisms. To bridge this gap, we invert a validated neural mass model of the corticothalamic system using scalp EEG collected during nonlinear transitions in conscious experience and sensory awareness across varying depths of dexmedetomidine sedation. We found that a decline in conscious experience and sensory awareness with dexmedetomidine was associated with a decrease in the engagement of excitatory thalamocortical loop resonances, along with an increase in inhibitory intrathalamic loop gains. These findings shed light on the neural mechanisms of conscious experience and sensory awareness, and offer a plausible explanation of how it fades across arousal states, bridging the gap between the neural correlates of consciousness and its underlying systems-level thalamocortical mechanisms.

FONDECYT de Inicio 11251578.

Energy Restriction Effects on Learning in a Computational Model of the Brain-in-a-Dish

Matías Urrea Cabezas[1,2], Camilo Jara Do Nascimento[1], Samuel Madariaga[1,2], Pedro Maldonado[1,2], Mircea Petrache[1,4,5], Rodrigo Vergara[1,2,3], Christ Devia[1,2]

(1) National Centre for Artificial Intelligence, Vicuña Mackenna 4860, Macul, Santiago, Chile
(2) University of Chile, Dept. of Neuroscience, Faculty of Medicine, Av. Independencia 1027, Independencia, Santiago, Chile
(3) Metropolitan University of Educational Sciences, Dept. of Kinesiology, Faculty of Arts and Physical Education, Av. José Pedro Alessandri 774, Ñuñoa, Santiago, Chile
(4) Pontificial Catholic University of Chile, Dept. of Mathematics, Faculty of Mathematics, Avenida Vicuña Mackenna 4860, Macul, Santiago, Chile
(5) Pontificial Catholic University of Chile, Mathematical and Computational Engineering Insitute

Biological neurons are remarkably energy-efficient, capable of performing complex computations with minimal energy consumption. Understanding these mechanisms can inform the design of efficient computational models and energy-aware learning systems. On this work, we developed a simulated environment/arena in NEST where a network of biophysically plausible artificial neurons control a two-wheeled robot that learns to avoid obstacles based on proximity sensor data. Specifically, for the simulations, we implemented energy-dependent neuron and synaptic plasticity models—Energy-Dependent Leaky Integrate-and-Fire (EDLIF) and Energy-Dependent Spike-Timing-Dependent Plasticity (EDSTDP). Our network, driven by synaptic plasticity, learned to steer away from obstacles based on sensory input. We further observed that, on this model, modifying ATP-related parameters significantly affected learning, suggesting that the task's success is closely tied to energy availability.

These results emphasize the role of metabolic constraints in learning and offer insights for the development of energy-efficient neuromorphic systems.

Funding: National Center for Artificial Intelligence CENIA, Basal ANID, Chile (FB210017)Powered@NLHPC: The supercomputing infrastructure of the NLHPC (CCSS210001)Exploration Project: Intelligence costs energy (13240026)

Noradrenaline and Acetylcholine shape Functional Connectivity organization of NREM substages: an empirical and simulation study

Fernando Lehue[1,2], Carlos Coronel-Oliveros[3,4], Vicente Medel[3], Thomas Liebe[5,6], Jörn Kaufmann[7], Sebastián Orellana[1,2], Diego Becerra[1,2], Enzo Tagliazucchi[3,8], Patricio Orio[1,9]

(1) Centro Interdisciplinario de Neurociencia de Valparaíso, Harrington 287, Valparaíso, Chile
(2) Universidad de Valparaíso, Programa de Doctorado en Ciencias, mención Biofísica y Biología Computacional, Gran Bretaña 1091, Valparaíso, Chile
(3) Universidad Adolfo Ibáñez, Latin American Brain Health Institute (BrainLat), Diagonal Las Torres 2640, Peñalolén, Santiago, Chile
(4) University of California San Francisco (UCSF) & Trinity College Dublin, Global Brain Health Institute (GBHI), California and Dublin, Ireland & US
(5) University of Jena, Department of Psychiatry and Psychotherapy, D-07743, Jena, Germany
(6) University Hospital Magdeburg, Department of Dermatology and Venerology, Leipziger Straße 44 39120, Magdeburg, Germany
(7) University of Magdeburg, Department of Neurology, D-39120, Magdeburg, Germany
(8) University of Buenos Aires, Buenos Aires Physics Institute and Physics Department, Intendente Güiraldes 2160, Buenos Aires, Argentina
(9) Universidad de Valparaíso, Instituto de Neurociencia, Facultad de Ciencias, Gran Bretaña 1091, Valparaíso, Chile

Sleep onset is characterized by a departure from arousal, and can be separated into well-differentiated stages: non-REM (NREM, encompassing N1, N2 and N3) and REM. Awake brain dynamics are maintained by various wake-promoting mechanisms, particularly the neuromodulators Acetylcholine (ACh) and Noradrenaline (NA), whose levels naturally decrease during the transition to sleep. The combined influence of these neurotransmitters on brain connectivity during sleep remains unclear, as previous models have examined them mostly in isolation or only in deep sleep. In this study, we analyze fMRI data obtained from healthy individuals and employ a Whole Brain model to investigate how changes in ACh and NA, affect the Functional Connectivity (FC) of the brain. FC analysis reveals distinct connectivity changes: a decrease in Locus Coeruleus (LC) connectivity with the cortex during N2 and N3, and a decrease in Basal Forebrain (BF) connectivity with the cortex in N3. Additionally, compared to Wakefulness (W), there is a transition to a more integrated state in N1 and a more segregated state in N3. We fit a Wilson-Cowan whole brain model model (informed with an empirical connectome and maps of modulation) to empirical BOLD FC, adjusting the coupling and input-output slope of the Whole Brain model to account for ACh and NA, respectively, and show that region-specific neurotransmitter effect is key to explain their effects on FC. This work enhances our understanding of neurotransmitters' roles in modulating sleep stages and their significant contribution to brain state transitions between different states of consciousness, both in health and disease.

Funding: Beca ANID de Doctorado Nacional 2022 (folio 21220708)

Cx43 hemichannels mediate purinergic signaling between odontoblasts like cells and trigeminal ganglion derived neurons in cariogenic conditions

Isaac E. Garcia[1]

(1) Laboratorio de Fisiología Molecular y Biofísica, Facultad de Odontología, Universidad de Valparaíso, Subida Carvallo 211, Playa Ancha, Valparaíso

Dentinal hypersensitivity is an intense pain response to normally innocuous stimuli. This has been proposed that odontoblasts, the main cells in the dental pulp, sense pain related stimuli since they express several ion channels able to sense mechanical, thermal, chemical, and to mediate intercellular communication. Odontoblast from human carious teeth overexpress connexin channels, however their role in dentinal hypersensitivity remains elusive. Here I used murine (MDPC-23 odontoblast like cells) and human odontoblast like cells exposed to lipopolysaccharides (LPS, 1 µg/ml) to interrogate the functional consequence of connexin overexpression in cariogenic conditions. I found that Cx43 is localized forming functional gap junction plaques in MDPC-23 favoring the coupling between neighbor odontoblasts. Exposure to LPS promotes a time dependent increment in the level of expression of Cx43. Biotynilation and dye uptake assays revealed that LPS favors the formation of functional free Cx43 hemichannels, rather than of gap junction plaques. In contrast, LPS exposure promotes a downregulation Panx1, a protein proposed to mediate a paracrine signal between odontoblast and dental primary afferents. Mechanical stimulation of single isolated odontoblast evokes Cx43-mediated both ATP release and transient calcium signals in cocultured neighbor trigeminal ganglion derived neurons. These results strongly suggest that Cx43 hemichannels are important players in the mechanism of dental nociception under cariogenic conditions.

Funding: CIDI#5 Universidad de Valparaíso

Differential Modulation of GlyRa3 by SEC8 Protein: Impact of Phosphorylation of Residue S346 on the interaction of SEC8 with the GlyRa3

Paul Soto Ortega[1], Santiago Quintana[1], Valentina De La Fuente[1], David Flaig[1], Jackson Delgado[1], Julianna Cossio[1], David Ramirez[1], Carlos Felipe Burgos[1], Carola Muñoz-Montesino[1], Gustavo Moraga-Cid[1]

(1) Universidad de Concepción, Departamento de Fisiología, Facultad de Ciencias Biológicas, Barrio Universitario, Concepción, Chile

The glycine receptor (GlyR) is a chloride ion channel from the pentameric ligand-gated ion channel (pLGIC) family, which includes nicotinic acetylcholine, serotonin type 3, and GABA type A receptors. GlyRs regulate neuronal excitability in the central nervous system (CNS), and their dysfunction is linked to hyperekplexia, autism, schizophrenia, epilepsy, and chronic pain. GlyRs consist of four α subunits (α1–α4) and one β subunit, each with an extracellular domain (ECD), transmembrane domain (TMD), and intracellular domain (ICD). The function of GlyRs can be modulated by external or endogenous allosteric modulators, and intracellular protein interactions or PKA-mediated phosphorylation events also allosterically influence GlyR function. The α3 subunit is enriched in the dorsal horn of the spinal cord and is involved in sensory processing, particularly nociceptive signaling. Notably, phosphorylation of residue S346 in the ICD of GlyRα3 has been linked to chronic pain. SEC8, a protein involved in the secretory pathway, interacts with the GlyRα3 ICD, but its effect on GlyR function, particularly in the phosphorylated state, remains unclear. Using biochemical, bioinformatic, and electrophysiological techniques, we investigated the GlyRα3–SEC8 interaction. Our results show that SEC8 differentially modulates glycine-activated currents in wild-type GlyRα3 and the S346E phosphomimetic variant. At the single-channel level, SEC8 prolonged open times and increased amplitude. These findings suggest a selective positive modulation of the phosphomimetic receptor by SEC8, highlighting the ICD as a potential therapeutic target for GlyR dysfunction-related disorders.

Funding: Fondecyt 1251488

Elucidating the de-activation and desensitization process of the glycine receptor α3 by neurosteroids

Santiago Quintana Herrera[1], Valentina De La Fuente[1], Paul Soto[1], David Flaig[1], Julianna Cossio[1], Jackson Delgado[1], David Ramirez[1], Carola Muñoz-Montesino[1], Gustavo Moraga-Cid[1]

(1) Universidad de Concepción, Departamento de Fisiología, Facultad de Ciencias biológicas, Barrio Universitario, Concepción, Chile

The glycine receptors are inhibitory ionic channels permeable to anions, belonging to the pentameric ligand-gated ion channels (pLGICs) superfamily. Electrophysiological and behavioral studies have reported the participation of the glycinergic transmission, mediated firstly by the GlyRα3, in processes like anxiety, depression and ethanol addiction, representing a critical target for research. It´s open probability and desensitization process is modulated by compounds like cannabidiol, propofol and neurosteroids. Neurosteroids are endogenous steroids synthesized by neurons with anesthetic and antidepressant effects. In this context, historically the $GABA_AR$ have been proposed as the main target for neurosteroids action in the central nervous system such as Allopregnanolone, approved by the FDA for post-partum depression. However, recent results suggest that neurosteroids can also modulate the function of the GlyRs compound by the subunit α3. Remarkably, GlyRα3 are expressed in brain regions associated with depressive states, playing a critical role in the control of neuronal excitability in these nucleuses like accumbens and amygdala.

Our previous results showed that Allopregnanolone enhances the function of GlyRα3 by 30%, but it´s molecular determinants have not been described at all. In the present work, using site directed mutagenesis and electrophysiological recordings, we evaluated the binding site of Allopregnanolone. Our results shows that W239 and A303 are crucial amino acids for the interaction of Allopregnanolone, with its main effects in the de-activation and desensitization state. These results contribute to the modulation of the GlyRα3 in the desensitization and de-activated states, being the TM1 and TM3 crucial for the allosteric modulation with therapeutic potential.

Funding: Fondecyt 1250880

Regulation of GABA type A receptors (GABAARs) through phosphorylation: Effects on receptor function and responsiveness to allosteric modulators.

David Flaig Lobos[1], Paul Soto Ortega[1], Camila Morel-Soto[1], Valentina De La Fuente Vega[1], Santiago Quintana Herrera[1], Carla Torres-Fuentes[1], Tamara Cáceres-Palma[1], Alejandra Fuentes-Garrido[1], Carola Muñoz-Montesino[1], Gonzalo Yévenes Crisóstomo[1], Gustavo Moraga-Cid[1]

(1) Universidad de Concepción, Departamento de Fisiología, Facultad de Ciencias Biológicas, Barrio Universitario S/N, Concepción, Chile

The gamma-aminobutyric acid type A receptors ($GABA_ARs$) belong to the pentameric ligand-gated ion channels (pLGICs) family. Fast inhibitory transmission in the brain is mediated mostly by $GABA_ARs$ with α1β2γ2 being the predominant subtype in the adult brain. The functional pentamer consists of five subunits arranged around a chloride-permeable pore, and each subunit contains an extracellular (ECD), transmembrane (TMD), and large intracellular domain (ICD). Their activity can be modulated by different protein kinases targeting serine residues in the ICD. Although multiple studies have reported that phosphorylation decreases the maximal currents of these receptors, the precise molecular mechanism remains debated. A leading hypothesis is that this effect results from a reduction in the channel's unitary conductance. To determine whether $GABA_ARs$ ICD phosphorylation by PKA affects the function of the α1β2γ2 receptor, we conducted electrophysiological recordings using whole-cell and single-channel configurations. Under phosphorylation state activated by 8-bromo-cAMP, the concentration-response curve showed a significant leftward shift, decreasing the EC_{50} without significantly changing the I_{max} recorded in whole-cell configuration. At single-channel level, the same condition produced a marked reduction in the unitary conductance of the channel. Remarkably, application of well-known positive allosteric modulators (PAMs), such as propofol and allopregnanolone partially restored the diminished unitary conductance. These findings support the critical role of phosphorylation in modulating the function $GABA_ARs$, as seen in others PLGICs family. This work aims to provide further insight into the intracellular regulation of these receptors, as many molecular, biophysical and structural aspects involved remain unclear.

Funding: Fondecyt regular 1251488 Gustavo Moraga Cid.Fondecyt regular 1250856 Gonzalo Yévenes Crisóstomo.

Zoledronic Acid Blocks TRPV1 Channels and Induces Analgesia

Cesar A. Amaya-Rodríguez[1,2,8], Karina Carvajal-Zamorano[1], Ana Gómez del Campo[3], Angelina Palacios[1,4], Nicolas Ardiles[1], Carlos Ancatén-González[1], Rodrigo C. Meza[5], Wladimir Plaza-Briceño[1], Ignacio Segura[1], Rosa Scala[6], Domenico Tricarico[7], Pablo R. Moya[1,5], Rodolfo Madrid[3], Andrés E. Chávez[1], Ramón Latorre[1], Karen Castillo[1]

(1) Universidad de Valparaíso, Centro Interdisciplinario de Neurociencia de Valparaíso, Facultad de Ciencias, Valparaíso, Chile
(2) Universidad de Panamá, Departamento de Fisiología y Comportamiento Animal, Facultad de Ciencias Naturales, Exactas y Tecnología, Ciudad de Panamá, Panamá
(3) Universidad de Santiago de Chile, Departamento de Biología, Facultad de Química y Biología, Santiago de Chile, Chile
(4) Universidad de Valparaíso, Centro de Investigación en Ciencias
Odontológicas y Médicas, Facultad de Odontología, Valparaíso, Chile
(5) Universidad de Valparaíso, Instituto de Fisiología, Facultad de Ciencias, Valparaíso, Chile
(6) Washington University, School of Medicine, Department of Cell Biology and Physiology and the Center for Investigation of Membrane Excitability Diseases, St Louis, Missouri, United States
(7) University of Bari, Department of Pharmacy-Pharmaceutical, Section of Pharmacology, Bari, Italy
(8) Universidad de Valparaíso, Programa de Doctorado en Ciencias Mención Biofísica y Biología Computacional, Facultad de Ciencias, Valparaíso, Chile

The transient receptor potential vanilloid 1 (TRPV1) channel, also known as the heat and capsaicin (CAP) receptor, is expressed in primary nociceptive neurons and play a central role in pain sensation and neurogenic inflammation. While CAP and its analogues can induce topical analgesia, their systemic use is limited by severe thermoregulatory side effects, driving the search for safer TRPV1 modulators. Zoledronic acid (ZOL) is a bisphosphonate widely prescribed to treat bone disorders, has been consistently associated with pain relief in patients, although the underlying mechanism remains unclear. In the present study, we utilize a combination of behavioral assays, Ca^{2+} imaging, and electrophysiological recordings to demonstrate that ZOL directly inhibits TRPV1 channel activity. *In vivo* ZOL administration reduced thermal nociceptive behaviors in both mice and *Drosophila* models.

In vitro, in dorsal root ganglion neurons ZOL suppressed CAP-evoked calcium responses, and membrane patches of Xenopus laevis oocytes, it significantly decreased TRPV1-mediated currents. Notably, the inhibitory effect was reversed by altering ionic strength asymmetry, suggesting a pore-blocking mechanism. This is the first study to report TRPV1 pore occlusion by ZOL, offering a novel mechanistic explanation for its analgesic effects in patients. In sum, the present findings identify ZOL as a potent TRPV1 inhibitor and elucidate a mechanistic basis for its antinociceptive action. These results underscore the potential of ZOL as a promising scaffold lead compound for the development of new TRPV1-targeted pain therapeutics.

Temporal associations of Slow Oscillations and local activity in distinct telencephalic areas of pigeons

Amanda Schuck Rodríguez[1], Máximo Fernández Villafaña[1], Jorge Mpodozis Marín[1]

(1) Universidad de Chile, Departamento de Biología, Facultad de Ciencias, Las Palmeras 3425, Ñuñoa, Santiago, Chile

Cortical slow oscillations (SOs) are spontaneous episodic oscillations of great amplitude and low frequency which appear during quiescent states, like non-REM sleep or deep anesthesia and were originally described in mammals. Sos appear to be coupled with faster oscillations and neuronal firing during its negative deflections. SOs propagate in the cortex due to intracortical connections, involving most of the cortical areas. Recently, comparable SO activity has been found in different areas of the telencephalon of birds,
including the dorsal ventricular ridge (DVR) and the Hyperpallium (H), during sleep and deep anesthesia. Interestingly, although they are anatomical distinct, DVR and H have both been proposed as possible avian cortical homologues. Even though both areas present apparent SOs, no work to date has studied a possible association between them. In this work we used simultaneous multiple recordings from anesthetized pigeons to analyze the temporal relation between the SO in the primary visual DVR, a second order visual DVR and the visual part of H. We analyzed the correlation between the SO and the local multi-unitary activity of each area and between areas. We found that SOs are temporarily associated between the visual areas of the DVR and H, although multi-unitary activity is not always correlated between them. We then classified the SOs based on the previous results and found at least two types of SOs regarding the involvement of each area. This study provides the first results showing an association of the SOs from these telencephalic areas of birds.
Funding: This work was funded by the Neurobiología y Biología del Conocer laboratory from the Science Faculty of the University of Chile. FONDECYT 1250880.

Theta modulation of hippocampal activity during distinct brain states.

Mauricio Caneo[1], Nelson Espinosa[1], Ariel Lara[1], Pablo Fuentealba[1]

(1) Pontificia Universidad Catolica de Chile, Psiquiatria, Medicina, Lira 40, Santiago, Región Metropolitana, Santiago, Chile

Theta oscillations in the brain play a pivotal role in coordinating behavior across different states. We characterized how distinct brain states (wakefulness and sleep) modulate theta oscillations and associated neural activity in the hippocampus (CA1d and DG) and subcortical regions (SuM, LS, and HyP). Using electrophysiological recordings, we found that theta power and frequency in CA1d and SuM are significantly higher during active exploration (AE) compared to REM sleep. Functional connectivity, evaluated through phase coherence, revealed increased synchrony between CA1d-SuM and SuM-DG pairs during AE. Spike activity exhibited higher firing rates during AE and quiet wakefulness (QW) compared to REM sleep, with stronger spike-theta coupling observed in REM sleep. Additionally, changes in theta power in CA1d, DG, LS, and HyP correlated with speed and acceleration during AE, indicating that these oscillations dynamically reflect locomotor parameters.

Our findings underscore how theta oscillations and neural activity adapt to different brain states to support sensorimotor integration and cognitive fucntions.

Funding: Project FONDECYT N° 1190375 (P.F.D) Project FONDECYT N° 1230589 (P.F.D) Project Anillo ACT 210053 (P.F.D)Scholarship ANID Doctorado Nacional 2019-21191573 (M.C.C)

Visual Pulvinar Responses in Mice: Implications for Prey Capture and Escape

Cristian Morales[1], Alfonso Deichler[1], Maricel Quispe[1], Gonzalo Marín[1]

(1) Universidad de Chile Laboratorio Neurobiología del conocer, Biología, Ciencias, Las Palmeras 3425, Santiago, Chile

Detection and avoidance of threats are essential features of instinctive defensive behaviors. In the visual domain, evidence indicates that the superior colliculus (SC) and its ascending tectofugal pathway are critical components of the neural circuitry orchestrating defensive maneuvers. Abnormal activation of this pathway may contribute to social phobias and anxiety disorders, highlighting the importance of understanding the neural mechanisms through which it detects threats and triggers adaptive responses. The functional roles of the SC's thalamic relays, the rostral (PulR) and caudal (PulC) visual pulvinar, remain poorly understood. In this study, we performed awake recordings in implanted mice. Histological analysis confirmed that recordings encompassed all major subdivisions of the visual thalamus. We identified units in both the dorsal lateral geniculate nucleus (DLG) and PulR that were modulated by the on–off phase of a grating stimulus; such phase-sensitive responses were absent in PulC. Units responsive to looming stimuli were found across all visual thalamic nuclei, but the temporal dynamics of modulation varied by region. Notably, PulC was the only nucleus whose peak response occurred before the stimulus reached maximum size. Additionally, PulC was the only visual thalamic region responsive to small moving square stimuli. Overall, these findings suggest that the two collicular-recipient zones, PulR and PulC, may be engaged in distinct behavioral functions, potentially reflecting specialized contributions to threat or prey detection and the visually guided behaviors associated with defensive and predatory actions.

Funding: Fondecyt posdoctorado 3220759Fondecyt 1210169

Dynamic Hippocampal-PFC circuit coupling underlies social recognition memory in a rat model

Catalina Herrada[1], Fernanda Millas[1], Alejandro Aguilera[2], Guillermo Lazcano[2], Mauricio Caneo[2], Nelson Espinosa[2], Pablo Fuentealba[2], Ariel Lara-Vásquez[1]

(1) Pontificia Universidad Católica de Chile, Departamento de Neurología, Facultad de Medicina - College UC, Santiago, Chile
(2) Pontificia Universidad Católica de Chile, Laboratorio de Circuitos Neuronales, Departamento de Psiquiatría, Facultad de Medicina, Santiago, Chile

Social recognition memory is the ability to identify and remember familiar conspecifics and is a core cognitive function essential for adaptive behavior in humans and animals. Disruptions in this capacity are a hallmark of several neuropsychiatric conditions, including schizophrenia and autism spectrum disorders. Although the hippocampus and prefrontal cortex (PFC) have each been independently linked to memory processing and social behavior, the mechanisms through which these regions coordinate during social memory formation remain largely unknown.

We hypothesize that the hippocampus and PFC engage in dynamic, context-dependent functional coupling, particularly via synchronized oscillations. We combined behavioral and electrophysiological approaches in freely moving rats to address this hypothesis. We implemented a modified social recognition task in a spatial arena to allow controlled evaluation of exploration behavior across familiar and novel conditions. Using custom-designed hyperdrives, we performed chronic recordings of local field potentials (LFPs) and single-unit activity from the dorsal and ventral hippocampus as well as the PFC.
We found that spontaneous spectral coherence in the hippocampal-PFC network was modulated by social novelty. Notably, dorsal hippocampus-PFC theta-band coherence decreased during the novel trial compared to the familiar trial ($p < 0.05$), while no significant differences were observed in ventral hippocampus-PFC coherence. Suggesting that novel social encounters may disrupt theta synchronization, potentially affecting the integration of contextual and social information. These dynamic, subregion-specific shifts in hippocampal-PFC communication may underlie distinct phases of social memory processing. Our findings have special relevance for identifying circuit-level targets to mitigate social and cognitive dysfunctions in neuropsychiatric disorders.

Funding: Fondecyt 1230589

Differential Dopaminergic Vulnerability and Mitochondrial Alterations over Aging in Drosophila melanogaster

Paula Amado[1], Jorge M. Campusano[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Av. Libertador Bernardo O' Higgins 340, Santiago, Chile

Dopaminergic neurons are strongly associated with age-related neurodegenerative diseases, including Parkinson's disease, and their impairment over aging has been associated with alterations in motor control. Notably, dopaminergic subpopulations show differential vulnerability, highlighting the complexity of their response to aging and pathology. Mitochondrial dysfunction is a hallmark of aging and neurodegeneration. Their spatial organization critically impacts function, and modulating mitochondrial dynamics has been shown to influence survival in animal models.

We examined whether age-related changes in locomotor performance are associated with dopaminergic cluster-specific neurodegeneration and used a fluorescent mitochondrial marker to assess the presence and distribution of mitochondria in dopaminergic neurons over time,

aiming to understand whether mitochondrial features contribute to their differential vulnerability.

The exponential phase of fly mortality began after 50 days post-eclosion, with females living up to 72 days and males up to 62 days. Basal locomotor activity declined at 30 days in both sexes, and their climbing ability decreased by day 40 in males and day 30 in females. We observed an overall decrease in dopaminergic neuron number across aging.

However, only the PPM3 cluster exhibited significant and cluster-specific neurodegeneration. These neurons, which project to the central complex – a brain region involved in motor control- also showed a marked reduction in somatic mitochondrial fluorescence at 60 days.

Our findings suggest that mitochondrial parameters are differentially altered across dopaminergic clusters during aging, potentially contributing to their distinct susceptibility and underlying effects on dopaminergic-related behaviors like motor control.

Funding: Supported by Fondecyt 1231556 (JMC) and ANID Doctoral Fellowship 21221779 (PAH)

Functional Dynamics of Visual Cortical Microcircuits in the Extra-Classical Receptive Field Effect: A Computational Model

Samuel Madariaga[1,2], Pedro Maldonado[1,2], Christ Devia[1,2]

(1) Universidad de Chile, Departamento de Neurociencia, Santiago, Chile
(2) Centro Nacional de Inteligencia Artificial (CENIA), Santiago, Chile

Contextual modulation in the visual cortex, driven by extra-classical receptive field (eCRF) effects like surround suppression, is a cornerstone of sensory processing. However, the underlying circuit mechanisms remain elusive, and existing models fail to replicate their quantitative properties. Therefore, this study aims to systematically dissect the relative contributions of lateral and hierarchical circuits; and to determine whether a biologically plausible architecture integrating lateral and hierarchical circuits is necessary to generate these effects. We developed a large-scale spiking network model of visual areas V1 and V2, implemented in NEST and based on the Potjans-Diesmann microcircuit. Our results demonstrate that a comprehensive model, integrating lateral connections within V1 and V2, alongside feedforward and feedback pathways between them, is uniquely capable of replicating a strong surround suppression (~75%). This value, consistent with physiological data, could not be achieved by simpler architectures lacking inter-areal competition. This finding suggests that robust suppression emerges from a competitive, winner-take-all-like dynamic between functionally distinct populations in higher cortical areas, rather than from local V1 circuits alone. Leveraging this validated platform and the extensive literature on excitatory/inhibitory (E/I) imbalance in schizophrenia, we then explored the model's applicability to circuit dysfunction. By selectively reducing the connectivity of layer 2/3 interneurons to simulate this condition.

The model successfully replicated key electrophysiological biomarkers, including pathological alterations in gamma-band oscillations during evoked activity. Summarizing, this work presents a mechanistic substrate for contextual modulation and offers a computational framework for investigating cortical circuit dysfunction.

Funding: The National Center for Artificial Intelligence CENIA, Chile (FB210017)Powered@NLHPC: The supercomputing infrastructure of the NLHPC (CCSS210001)Exploration Project: Intelligence costs energy (13240026)

Enlarged perivascular spaces as a marker of impaired glymphatic system: evidence from the ReDLat consortium

Ana Maria Castro Laguardia[1], Florencia Altschuler[2], Daniel Franco O´Byrne[1], Agustín Ibañez[1,3,4], Cecila González Campo[2], Vicente Medel[1]

(1) Universidad Adolfo Ibáñez, Latin American Brain Health Institute, Facultad de Psicología, Diagonal Las Torres 2640, Santiago, Chile
(2) Universidad de San Andrés, Centro de Neurociencias Cognitivas, Vito Dumas 284, B1644BID Victoria, Buenos Aires, Argentina
(3) University of California San Francisco, Global Brain Health Institute (GBHI), 675 Nelson Rising Lane, Suite 190, San Francisco, CA, United States
(4) Trinity College Dublin, College Green, Dublin 2, Dublin, Irlanda

Background: Enlarged perivascular spaces (PVS) have emerged as potential neuroimaging markers of impaired glymphatic clearance and small vessel dysfunction. However, their systemic and social correlates remain underexplored, particularly in diverse populations. Objective: Here, we aimed to characterize the total PVS volume across the spectrum of healthy aging and neurodegeneration, and to examine its associations with cardiometabolic risk factors in a large, socio-culturally diverse sample of older adults from Latin America and the United States. Methods: We analyzed data from 1522 participants in the ReDLat consortium, including cognitively normal individuals and patients with Alzheimer's disease (AD) and frontotemporal dementia (FTD). PVS were quantified using an automated, deep learning–based segmentation approach on T1-weighted MRI images.

Cardiometabolic variables (body mass index, blood pressure, and heart-rate variability) were systematically assessed. Results: In preliminary analyses, the total PVS volume was significantly higher in older adults (≥60 years) compared to younger controls ($p = 0.00000003467$), and increased in the groups with dementia compared to controls ($p < 0.00001$). We also expect that a higher cardiometabolic burden is independently associated with increased PVS volume. Conclusion: Our findings add to the idea of enlarged PVS volumes as proxies of the converging effects of aging, neurodegeneration, cardiometabolic dysfunction, and social adversity on brain health. These results potentially support the relevance of PVS as a promising imaging marker to capture the relationship between biological and social mechanisms of brain vulnerability in older adults from diverse backgrounds.

Funding: This work is supported by FONDECYT de Inicio 11251578 and ReDLat Consortium. The first author is funded by an Excellence Doctoral Fellowship from Adolfo Ibáñez University, with event participation partially funded by an IBRO-SNC grant.

Neuronal Distribution and Physiological Responses of Transient Receptor Potential (TRP) and ATP Receptors (P2X) in the Mouse Nodose Ganglion (NG).

Julio Alcayaga[1], Josefina Lewin[1,2], Pedro Piquer[1,2], Elías Utreras[1,2]

(1) Universidad de Chile, Biology, Cell Physiology and Neurobiology Laboratory, Sciences, Las Palmeras 3425, Santiago, Chile
(2) Universidad de Chile, Biology, Cellular and Molecular Mechanisms of Pain Laboratory, Sciences, Las Palmeras 3425, Santiago, Chile

The nodose ganglion (NG) hosts most vagal sensory neurons, innervates most internal organs and glands, and conducts sensory activity to the CNS, which elicits homeostatic reflexes. Transduction mechanisms in these neurons encompass a series of membrane receptors and ion channels, activated directly or by signaling molecules released into the extracellular medium. Transient receptor potential (TRP) channels, both ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1), and ionotropic ATP receptors (P2X) are present in NG neurons, generating afferent activity in some sensory modalities. However, there is no robust information on the neuronal distribution of these different channels and receptors in the whole NG. Using immunostaining techniques and extracellular nerve recordings, we characterized the distribution of TRPA1, TRPV1 channels, P2X receptors, and the responses evoked by specific agonists applied to the NG. TRPA1, TRPV1, and P2X2 receptors were conspicuously present in most NG neurons, although with different immunohistochemical signal intensity. Moreover, most neurons presented both TRP channels signal simultaneously, as well as the P2X2 receptor. In the in vitro NG-vagus nerve preparation, application of ATP to the NG briefly increased nerve discharge, in a dose-dependent manner, both in amplitude and duration. Applications of capsaicin (a TRPV1 agonist) and allyl isothiocyanate (AITC, a TRPA1 agonist) produced a long-lasting increase in the nerve discharge, which was dose-dependent but of smaller amplitude than those evoked by ATP. Our results indicate that TRP channels and P2X receptors coexist in NG neurons, and that their exogenous activation increases the activity of a large population of NG neurons.

Funding: ANID-FONDECYT 1240611

Early thalamic input does not influence the establishment of the visual DVR in birds.

María José Rojas Bascuñán[1], Rosana Reyes-Pinto[1,2], Jorge Mpodozis[1]

(1) Universidad de Chile, Biologia, Ciencias, Las Palmeras 3425, Ñuñoa, Chile
(2) Centro de Biología Integrativa (CIB), Universidad Mayor, Chile

The evolutionary homology of the neocortex remains widely debated. In mammals, the sensory pallium is organized into a six-layered neocortex, with layer 4 receiving direct, topographic thalamic input. This input is essential for assembling cortical territories and establishing functional circuits, guiding both structure and connectivity during development. In birds, the sensory pallium comprises the dorsal ventricular ridge (DVR), a trilaminar complex including thalamorecipient, efferent, and associative layers. These layers are interconnected by local circuits organized according to a columnar and reciprocal motif. Whether in birds, as in mammals, thalamic sensory input instructs DVR development remains unclear. We have previously investigated this question in chicks using as study subject the tecto-visual DVR (vDVR). We found that thalamo-vDVR and intra-vDVR connections emerge concurrently at a very early stages, between embryonic days 6–8 (E6–E8).

We also preliminarily tested the role of retinal input and found that eliminating visual activity throughout embryogenesis did not disrupt vDVR circuit development. To test whether thalamic input (from nucleus Rotundus), influences vDVR development, we performed targeted in ovo lesions to eliminate Rt afferents, before they reached the vDVR. Neurofilament immunohistochemistry and tracer injections between E8–E12 revealed that vDVR circuits developed normally, preserving columnar and topographic organization. vDVR cytoarchitecture and size were unaffected, and Satb2 expression maintained its spatiotemporal pattern. These findings suggest that early vDVR specification and circuit formation are primarily governed by intrinsic pallial programs, independent of visual and thalamic input. This highlights a key developmental divergence in sensory circuit formation between mammals and birds.

Funding: FONDECYT REGULAR 1210069. FONDECYT REGULAR 1250880.

POSTER SESSION II

Preliminary Evidence of Slit-2/Robo-1-Induced Migration and EMT-Associated Changes in Glioblastoma

Javiera Sanzana Rosas[1,2], Yerko Rivas[2], Sebastian Azocar[2], Maria Paz Castillo[2], Felix Duprat[2], Paolo Pampaloni[2], Anyela Durán[2], Gabriel Olivas[2], Romina Bertinat[1], Ivan Gonzalez-Chavarria[2], Nery Jara[1]

(1) Universidad de Concepción, Farmacología, Ciencias Biológicas, Barrio universitario S/N, Concepción, Chile
(2) Universidad de Concepción, Fisiopatología, Ciencias Biológicas, Barrio Universitario S/N, Concepción, Chile

Glioblastoma (GBM) is the most aggressive primary brain tumor, characterized by extensive cell migration and invasion that contribute to therapeutic resistance and poor prognosis. The Slit-2/Robo-1 signaling pathway, originally described in axon guidance, has been implicated in tumor cell motility; however, its role in GBM remains controversial. In this study, we investigated the paracrine effects of Slit-2 on cell migration and epithelial-to-mesenchymal transition (EMT)-like features in human GBM cells.
Using U87 and U251 glioblastoma cell lines, we assessed their migratory response to exogenous recombinant human Slit-2 (rhSlit-2) in Transwell assays. Both cell lines exhibited directional migration and a chemorepulsive response, suggesting a chemotactic effect. Basal expression of ROBO1 was confirmed by Western blot, whereas SLIT2 expression was not detected in either line. To further explore the relationship between Slit-2 signaling and invasive behavior, we analyzed EMT-associated markers by Western blot and RT-qPCR. Slit-2-treated cells showed increased expression of vimentin and Slug, consistent with a shift toward a mesenchymal-like phenotype.

Additionally, transmigration assays confirmed a directional migration away from the Slit-2 source, supporting a potential guidance mechanism. These findings suggest that paracrine Slit-2 promotes directional migration and EMT-like features in GBM cells, challenging the conventional view of Slit-2 as a tumor suppressor in this context.
Our results provide preliminary evidence that the Slit-2/Robo-1 axis may contribute to glioblastoma invasion through guidance-like cues. Ongoing studies aim to determine whether these effects are Robo-1 dependent and whether similar behaviors occur in more physiologically relevant models.

Funding: Beca ANID. N° Folio 21242518Fondecyt Regular 1231911VRID 2023000857

Administration of a cyclic ketogenic diet improves motor performance and alters muscle organization in aged animals.

Jessica Mella Castro[1,2,3,4], Gabriel Quiroz[3], Francisca Bermedo-García[1], Pamela Pino[1], Diego Acuña-Catalán[2,3], Christian González-Billault[2,3,4], Juan Pablo Henríquez[1]

(1) Neuromuscular Studies Laboratory (NeSt Lab), Instituto de Anatomía, Histología y Patología, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile
(2) Cellular and Neuronal Dynamics Lab (CENEDYN), Department of Biology, Faculty of Sciences, Universidad de Chile, Santiago, Chile
(3) Center for Geroscience, Brain Health, and Metabolism (GERO), Universidad de Chile, Santiago, Chile
(4) Department of Neuroscience, Faculty of Medicine, Universidad de Chile, Santiago, Chile

Aging is associated with structural and functional decline of the neuromuscular junction (NMJ), the peripheral synapse responsible for muscle contraction. Caloric restriction (CR) extends lifespan and mitigates NMJ degeneration in animal models. Similarly, cyclic ketogenic diets (cKDs) elevate ketone body levels, supporting metabolic and neuroprotective functions. cKD also demonstrates improved adherence. While cKD improves cognition and memory in aged animals, its effects on aged skeletal muscle and NMJ structure remain unclear.
Aged mice (24 m.o) were fed either a cKD or control diet for 6 months. Body weight, blood glucose, and serum ketone bodies were measured. Motor performance was assessed using rotarod, inverted screen, grip strength, and electromyography (EMG). NMJ morphology and receptor dynamics were evaluated after immunostaining of motor axons and acetylcholine receptors (AChRs). Muscle histology and the expression of AChR subunits and rapsyn were also analyzed.
We found that prolonged cKD did not alter body weight or blood glucose levels but significantly increased serum ketone bodies. cKD improved motor performance, as shown by enhanced rotarod and inverted screen tests. However, no significant changes were observed in grip strength or compound muscle action potentials (CMAPs), suggesting that force generation was unaffected. Muscle analysis showed a shift toward slow-twitch fibers and reduced fiber size. Decreased expression of the NMJ scaffolding protein rapsyn correlated with altered AChR dynamics, despite unchanged NMJ morphology.
These results suggest that cKD promotes functional benefits in aged muscle through mechanisms independent of overt NMJ remodeling, potentially involving shifts in muscle fiber phenotype and synaptic protein regulation.

Funding: Fondecyt 3240731 (JM), 1221213 (JPH), 1220414 (CG-B), FONDAP 15150012 (CG-B)

Synergistic interaction between Fat3 and PTPsigma in retinal lamination

Monserrat Irarrazabal Figueroa[1], Eliseo N. Bustos[1], Evelyn C. Avilés[1], Marcela Paz González[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Alameda 340, Santiago, Chile

The formation of polarized neuronal circuits depends on events such as cell migration, neurite retraction, and precise location of synapses. The correct stratification of the retina, a structure of the central nervous system, into neuronal and synaptic layers is crucial for visual processing. The atypical cadherin FAT3 is a key coordinator of these cellular processes in retinal amacrine cells and thus retinal lamination. PTPσ, a protein tyrosine phosphatase receptor, is involved in axonal guidance and synaptogenesis in the brain. Our previous work shows that its absence does not affect

early retinal cell migration, but it does generate defects in later stages of development. Although a Fat3-PTPσ molecular interaction has been shown, their functional interaction and possible participation in a common molecular pathway for retinal lamination has not been elucidated. This work seeks to determine whether proper retinal lamination occurs through a synergistic or independent action of both components. The genetic interaction between Fat3 and Ptprs was analyzed using double knockout (dKO) and double heterozygous mouse models. The analysis of double heterozygous animals was used to see if their genetic interaction is functionally relevant. The phenotype in dKO mice ($Fat3^{-/-}$;$Ptprs^{-/-}$) presented a massive and synergistic disorganization of the retina, with total loss of stratification and the presence of generalized ectopic synapses. The distinct phenotypes of the individual mutants and the defect of dKO suggest that FAT3 and Ptprs do not act linearly in the same pathway, but rather on parallel but convergent pathways.

Analysis of NPY-Expressing Neurons in the Mouse Amygdala: Morphological and Synaptic Characterization and Response to Social Isolation

María Jesús Ulloa Schneeberger[1], Paulina Yañez[1], Camila Ramirez[1], María de los Ángeles Garcia[1], Antonia Recabal-Beyer[1]

(1) Universidad de concepción, Biologia Celular, Ciencias Biológicas, Edmundo Larenas 219, Concepción, Chile

Chronic stress has emerged as a key factor contributing to the global rise in obesity. Numerous studies show that individuals exposed to high levels of stress have a 25% to 40% higher risk of developing obesity. In the central nervous system, the hypothalamus, particularly the arcuate nucleus (ARC), regulates food intake, activating neurons that secrete orexigenic peptides such as neuropeptide Y (NPY). NPY is also expressed in limbic regions like the amygdala, involved in stress responses and the hedonic regulation of appetite. Activation of NPY circuits in the central (CeA) and medial (MeA) amygdala has been linked to the prioritization of feeding over other adaptive behaviors, as well as responses to abstinence. Notably, increased NPY in the amygdala has an anxiolytic effect that appears sex-dependent under stress conditions, although structural and numerical differences in NPY-expressing neurons in the CeA and MeA remain unclear.
Social isolation, recognized as a form of chronic psychosocial stress, induces alterations in brain regions such as the amygdala, with sex-specific effects. While NPY plays a protective role against stress, its expression in the amygdala in response to social isolation is not fully understood. Using a transgenic NPY-EGFP mouse model, this study examines sex differences in morphology, synaptic connectivity, and NPY expression in amygdala neurons under both baseline conditions and after social isolation.
This research seeks to deepen understanding of the neurobiological and sex-specific mechanisms linking stress to emotional regulation of appetite, highlighting NPY in the amygdala as a potential mediator between social isolation and vulnerability to obesity.

Funding: FONDECYT 11240516

Distribution of the vasoactive intestinal peptide receptors VPAC1 and VPAC2 and their relationship with dopaminergic amacrine cells in the mouse retina

Felipe Tapia[1], Ricardo Céspedes[1], Paulina Puebla[2], Ramón Sotomayor[3], Oliver Schmachtenberg[2]

(1) Universidad de Valparaíso, Centro Interdisciplinario de Neurociencia de Valparaíso, Gran Bretaña 1111, Valparaíso, Chile
(2) Universidad de Valparaíso, Instituto de Biología, Gran Bretaña 1111, Valparaíso, Chile
(3) Universidad de Valparaíso, Instituto de Fisiología, Gran Bretaña 1111, Valparaíso, Chile

Myopia is a common refractive error, whose prevalence is steadily increasing worldwide. Despite this, the knowledge regarding the mechanisms underlying myopia in mammals is fragmentary, with dopamine proposed as the main retinal output signal. On the other hand, recent research has shown vasoactive intestinal peptide (VIP) as a promising molecule in charge of signaling image defocus, the input signal of myopia pathogenesis. VIP is known to be produced in the retina and VIP agonism counteracts myopia, but the retinal location of the VIP receptors (VPAC1 and VPAC2) is not fully known. In this study, the precise location of VIP receptors within the retina was studied using immunofluorescence in mouse retinal slices with antibodies for VPAC1 and 2, and a possible co-localization with dopaminergic amacrine cells was studied with an anti-tyrosine hydroxylase antibody. VPAC1 was found in a subset of photoreceptor cells, morphologically compatible with cones and within the inner nuclear and ganglion cell layers. Multiple puncta in the stratum 1 of the inner plexiform layer were observed, in close proximity with dopaminergic amacrine cell varicosities. VPAC2 was found at the base of the photoreceptor outer segments, in putative photoreceptor synaptic terminals, and as a band in the middle of the inner plexiform layer. No clear co-localization was observed with tyrosine hydroxylase. The data obtained shows VIP receptors to be widely expressed in the retina, notably in both main synaptic layers. Further study will be focused on the circuitry associated with these receptors and their role in myopia.

Funding: ANID FONDECYT #3240404 (FT), #124-0141 (RS), #1210790 (OS), DOCTORADO #21241487 (RC).

Mitochondrial Nucleoid Distribution and Dynamics

Catalina Muñoz Muñoz[1], Josefa Macuada[1], Paula Amado[1], Constanza Vásquez-Venegas[2], Matías Berasain[2], Mauricio Cerda[2], Jorge Campusano[1], Verónica Eisner[1]

(1) Pontificia Universidad Católica de Chile, Faculty of Biological Sciences, Alameda 340, Santiago, Chile
(2) Universidad de Chile, SCIAN Lab, ICBM, Faculty of Medicine, Av. independencia 1027, Santiago, Chile

Neurons are specialized cells with high energetic requirements for maintaining their structure and for generating and propagating action potentials. One of the primary sources of ATP is the mitochondrion, an organelle that contains its own genetic material, known as mtDNA. The mtDNA encodes 13 proteins of the OXPHOS system and is packaged in nucleoids (DNA-protein complexes). The nucleoid distribution is relevant for replicative and damaged mtDNA segregation upon mitochondrial fission, and is altered in

the skeletal muscle of patients with mitochondrial disease. In addition, it has been reported that nucleoids exhibit dynamics inside mitochondria. Mutations in POLG, the mitochondrial DNA polymerase, accumulate mutated mtDNA and cause neurological diseases, where a heterogeneous distribution of damaged mtDNA at the tissue and cell levels in muscle samples has been reported. There is no information about mitochondrial nucleoid features in neurons, and whether nucleoid distribution is altered in neurons of POLG-carrying individuals remains unexplored. This work aims to begin characterizing the distribution and dynamics of nucleoids in the neuropile of control neurons and a Drosophila POLG mutant.

Funding: Supported by Fondecyt 1231556 (Jorge Campusano) and 1231557 (Verónica Eisner) and by ANID Doctoral scholarship 21222104 (Catalina Muñoz).

PTPsigma Regulates Amacrine Cell Positioning and Synapse Localization in the Developing and Mature Retina.

Eliseo Bustos[1], Monserrat Irarrázabal Figueroa[1], Marcela Paz González[1], Evelyn C. Avilés[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Alameda 340, Santiago, Chile

Functional neural circuit assembly depends on coordinated cell migration, neuron positioning and synapse formation and localization. Tissue polarity proteins direct these processes by orienting cells in the complex environment of the developing tissue.
The Type-IIA Receptor-type Protein Tyrosine Phosphatase (RPTP) family of proteins have been identified as synapse organizers. Additionally, the fly ortholog of PTPsigma, a member of this family, directs cell protrusions during collective cell migration. The implication of PTPsigma in both synapse formation and cell migration makes it an ideal candidate to regulate tissue polarity establishment during central nervous system (CNS) development.
The retina is a highly organized neural circuit that serves as a powerful model for studying CNS development. Different neurons, such as amacrine cells, must migrate and reach the correct final position in the laminated retina, and subsequently develop synapses. Defects in these processes often result in abnormal retinal lamination.

The aim of this work is to assess the role of PTPsigma in the organization of the retina and to elucidate whether earlier developmental defects in amacrine cell migration and positioning result in abnormal lamination in the mature system. The methodology consists of immunofluorescence analysis of amacrine cell positioning, and synapse localization in Ptprs$^{-/-}$ (PTPsigma knock-out) mouse retina compared to Wild-type littermates. The results show that PTPsigma is not necessary for amacrine cell migration in early development, but it does impact amacrine cell positioning and synapse localization in the developing and mature retina, possibly in an activity-dependent manner.

Funding: Proyecto Fondecyt de Iniciación código 11241253IBRO Rising Stars AwardStart-Up Fund UC

Relationship between Visual Scanning and Facial Emotion Recognition in Children with Disorders Characterized by Difficulties in Emotion Recognition

Amanda Silva-Maureira[1], Nicolás Balmaceda Pascal[1], Samuel Madariaga[1,2], Christ Devia[1,2]

(1) Universidad de Chile, Departamento de Neurociencia, Medicina, Santiago, Chile
(2) Centro Nacional de Inteligencia Artificial (CENIA), Santiago, Chile

Visual scanning patterns are key to recognizing facial emotions, and in populations with Attention-Deficit/Hyperactivity Disorder (ADHD) and Anxiety Disorders (AD), fixations have been described as shorter and more dispersed, which could negatively affect performance. This study examined whether these characteristics are associated with poorer emotion recognition.
We analyzed 9 children (6 ADHD/AD, 3 AD, 1 ADHD; aged 6–14 years) with eye-tracking data while identifying six basic emotions. Fixation duration and location within regions of interest (ROI: eyes, nose, and mouth) and outside these areas were measured, with a particular focus on short fixations (first quartile).
Overall performance varied by emotion (χ^2, $p < 0.001$): Surprise and Happiness showed the highest accuracy, while Anger and Disgust had the most errors. Anger and Fear had higher percentages of external fixations ($p < 0.01$), indicating a more dispersed visual pattern. However, the hypothesis that a higher proportion of short and dispersed fixations is associated with poorer performance was not confirmed globally: significant correlations were only found for Disgust ($r = –0.70$; $p = 0.043$) and, in the eye region, for Happiness, Disgust, and Anger.
These findings suggest that although, for certain emotions, short and dispersed fixations may be linked to lower accuracy, performance in children with ADHD and/or AD also seems to depend on other attentional and emotional factors specific to the type of expression.

From Development to Aging: Distinct Cell-Specific Contribution of Transglutaminase in the Central Nervous System

Joaquín Almonacid Torres[1], Isidora Almonacid[1], Jorge M Campusano[1], Carlos Oliva[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Santiago, Chile

Transglutaminases (TGs) are a family of 8 active enzymes capable of catalyzing calcium-dependent transamidation reactions, generally resulting in crosslinking and post-translational modifications of proteins.
Among them, the most studied is Transglutaminase 2 (TG2), which is ubiquitously expressed in mammal tissues. It has diverse functions in cellular processes, including adhesion, migration, growth, proliferation, differentiation, survival and apoptosis. In the central nervous system (CNS), evidence suggests that TG2 is involved in brain disorders, neurodegenerative diseases and brain injury.
However, little is known about the role of other TGs in CNS. Also, we don't know if these TGs may play distinct roles in different cellular types or processes like neurodevelopment or aging of the CNS.

Considering that at least 5 TGs are expressed in the mammalian brain, it is difficult to study their role in human or murine CNS. In this context, Drosophila melanogaster is a convenient model to study the function of these enzymes since it only has one TG encoding gene (dTg).
In this research, we used Drosophila melanogaster to study deficiency of dTG through the expression of RNAi only in neurons or glial cells, and exclusively during development or adulthood. Thus, we were able to assess the effects of dTG knock-down in a cell-specific manner during CNS neurodevelopment or aging. Basal locomotion and olfactory assays were performed on these animals. Additionally, we used immunostaining to evaluate the number of brain dopaminergic neurons in these flies. Our preliminary data indicate differential effects of dTG loss depending on cell type during aging.

Funding: Funded by Fondecyt grants 1231556 (Jorge Campusano) and 1231685 (Carlos Oliva)

Modulating Relapse Vulnerability in Addictive-Like Behaviors: The Role of Lactobacillus reuteri Supplementation in a Maternal Obesity Mouse Model

Macarena Moreno[1], Martina Oyarzún[1], María Paz Moreno[2], Daniel Moraga[2], Georgina Renard[3], Omar Porras[1]

(1) Universidad de Chile, Instituto de Nutrición y Tecnología de los Alimentos, Laboratorio de Nutrición Funcional, Av Macul 5540, Macul, Chile
(2) Universidad de Valparaíso, Laboratorio de Tecnología Farmacéutica, Farmacia, Av Gran Bretaña 1093, Valparaíso, Chile
(3) Universidad de Santiago, Centro de Investigación Biomédica Aplicada, Medicina, Av. Alameda Libertador Bernardo O'Higgins, 9170022, Estación Central, Chile

Maternal obesity has been associated with neurodevelopmental alterations that increase the risk of neuropsychiatric disorders in offspring, including greater vulnerability to addictive behaviors. However, the neurophysiological mechanisms involved and the preventive potential of interventions targeting the microbiota have been little explored. The present study evaluated the impact of maternal obesity on vulnerability to relapse in a murine model of conditioned place preference (CPP) to amphetamine (AMPH), as well as the modulatory effect of Lactobacillus reuteri supplementation during pregnancy and lactation. A high-fat diet (HFD)-induced obesity model and a control group fed a standard diet (CD) were used. During pregnancy and lactation, a subgroup of females received oral supplementation with L. reuteri. During adolescence and adulthood, the offspring were evaluated using the CPP to AMPH, recording the acquisition of preference, its extinction, and relapse after re-exposure to the drug. The offspring of obese mothers showed a significant increase in vulnerability to relapse in both stages, compared to controls ($p < 0.05$). This effect was attenuated in the groups whose mothers received L. reuteri ($p < 0.05$). No differences were observed in preference acquisition, suggesting a specific effect on relapse. These findings support the potential of microbiota modulation as a preventive strategy from the early stages of development and point to possible mechanisms of neuroprotection against critical stressors, such as drug exposure.

Financing: FONDECYT POSTDOCTORADO FOLIO 3240669

Drosophila lethality and behavioral effects induced by changes in expression of tyrosine hydroxylase in glial cells.

Fabiola Otárola[1], Jorge M. Campusano[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Santiago, Chile

Dopamine is a neurotransmitter critical for many body functions. Its synthesis is driven by tyrosine hydroxylase (TH), which catalyzes the rate-limiting conversion of tyrosine to L-DOPA. TH deficiency lowers dopamine, impairing motor behavior in organisms such as Drosophila. Glial cells uptake and inactivate aminergic transmitters —including dopamine—modulating its extracellular levels. Thus, by modulating dopamine extracellular levels, glial cells could contribute to locomotion in Drosophila. Interestingly, Drosophila RNA-seq databases support that glial cells express mRNA for TH. Whether a putative glial-expressed TH plays a role in locomotion is an open question we began evaluating here. Transgenic flies for the UAS-Gal4-Gal80^{ts} system were used during this research, to conditionally express RNAi against TH during development and only in glia. These experiments were aimed at evaluating whether the decrease in TH in glia could affect locomotion, in single female or male flies. Strikingly, the results obtained show that the expression of RNAi for TH in Drosophila glia during development results in a lethal phenotype, as no animals were obtained. Furthermore, mild RNAi expression allows for the generation of flies that exhibit changes in locomotion, which depends on the sex and age of flies. This suggests that the TH enzyme expressed in glial cells plays a key role during development, regulating fly development, eclosion from the pupal case and adult behavior. Future studies will seek to delve into these effects.

Funding: Supported by Fondecyt 1231556

Retinal Structural Alterations and Their Association With Cognitive Impairment in Individuals Living With HIV

Natalia Medina Munizaga[1], Maite Riquelme Quezada[1], Daniela Castillo[1], Ivan Plaza Rosales[1,2]

(1) Universidad de Chile, Department of Medical Technology, Faculty of Medicine, Av. Independencia 1027, Santiago, Chile
(2) Universidad de Chile, Laboratorio de Neurosistemas, Department of Neurosciences, Faculty of Medicine, Av. Independencia 1027, Santiago, Chile

Background: Advancements in health-related scientific research on Human Immunodeficiency Virus (HIV) have led to documented epidemiological changes in the course of the disease. Specifically, the introduction of antiretroviral therapy (ART) has resulted in a global reduction in HIV-related mortality, transforming the infection into a chronic condition. Alongside the associated increase in life expectancy, new clinical challenges have emerged. Among these, the incidence of retinal alterations and their potential correlation with HIV-associated neurocognitive Disorders (HAND) has become a growing area of interest in both clinical practice and public health.

The primary objective of this study is to determine the relationship between retinal structural changes and cognitive impairment in individuals living with HIV. We hypothesize that the thinner the retina—whether in specific layers or overall structure—the lower the cognitive performance in people living with HIV.

Methods: Participants in our study will be classified into two groups (individuals living with HIV and healthy HIV-negative controls). All subjects will undergo an analysis of retinal parameters using Optical Coherence Tomography (OCT), and an assessment of their cognitive performance through neurocognitive tests adapted and validated for the Chilean population (IFS-Ch, ACE-III). Data will be analyzed using linear regression modeling, descriptive statistics, and group comparisons.

Results: We expect to find a greater magnitude of structural alterations in the retina in people living with HIV who perform poorly on cognitive tests.

Conclusion: This study proposes a non-invasive screening, diagnostic, and monitoring strategy that allows periodic assessment of cognitive changes in individuals living with HIV through the analysis of retinal structure.

Pupil Dynamics Reflect Prediction Error and Cognitive Load During Multiple Object Tracking.

Andrea Hualme[1], Tomás Bosch[2], Tomás Ossandón[2]

(1) Pontificia Universidad Católica de Chile, Av. Libertador Bernardo O'Higgins 340, Santiago, Chile
(2) Pontificia Universidad Católica de Chile, Departamento de Psiquiatría, Facultad de Medicina, Marcoleta 381, Santiago de Chile, Chile

Prediction error (PE) reflects the mismatch between expected and actual outcomes, engaging the locus coeruleus–norepinephrine (LC-NE) system to modulate arousal and facilitate learning. Pupil dilation, a reliable peripheral marker of LC-NE activity, provides insight into cognitive effort and internal performance monitoring. This study examined how PE is encoded in pupil responses during a Multiple Object Tracking (MOT) task, which requires sustained and divided attention, with attentional load systematically varied (tracking 2, 3, or 4 targets). The MOT paradigm offers continuous cognitive engagement and precise error detection, making it well suited to study PE dynamics.

We hypothesized that pupil responses would reflect PE differently across difficulty levels. Pupil traces revealed three consistent phases: initial constriction at stimulus onset, gradual dilation during tracking, and a sharp peak at response. Crucially, errors (PE = 1) elicited a second, delayed dilation peak (~1.4 s post-response), which was absent or reduced in correct trials (PE = 0). This effect was robust across participants (n = 23) and significant at all load levels: 2 targets ($p = 0.023$), 3 targets ($p = 0.035$), and 4 targets ($p = 0.01$). Additionally, under high load, correct trials showed sustained dilation, suggesting internal reinforcement and sustained engagement.
These findings demonstrate that pupil dynamics reflect not only cognitive demand but also outcome evaluation and adaptation. Pupillometry thus serves as a sensitive, non-invasive index of real-time prediction error and attentional regulation in demanding cognitive contexts.

Funding: Proyecto FONDECYT regular N°1230383

EEG Microstate Dynamics During Visual Mental Imagery

Mario Villena-González[2], Deysha Poyser[1], Juan Alliende[1], German Campos-Arteaga[2], Felipe Rojas-Thomas[3], Juan-Pablo Morales[4]

(1) Pontificia Universidad Católica de Chile, Psicología, Ciencias Sociales, Santiago, Chile
(2) Universidad Tecnológica Metropolitana, Departamento de Ciencias Jurídicas y Sociales, Facultad de Ciencias Jurídicas y Sociales, Santiago, Chile
(3) Universidad Adolfo Ibañez, Center for Social and Cognitive Neuroscience (CSCN), Escuela de Psicología, Chile
(4) University of Sydney, Business School University of Sydney, Darlington, Australia

Visual mental imagery is a core process in imagination, memory, and aesthetic experience, involving the interplay of perceptual, mnemonic, and affective brain networks. EEG microstate analysis enables the characterization of the spatio-temporal organization of brain activity through transient topographical patterns, providing a framework to examine how the content and affective impact of an image modulate its mental representation. This study analyzes microstate patterns during tasks that require the mental reconstruction of visual scenes, varying in modality (visual imagery, discursive imagery, or external attention) and in affective load (high versus low emotional impact). This approach allows for the identification of how microstates associated with attentional and episodic memory networks are reorganized depending on the nature of the content and its emotional relevance. It is anticipated that scenes with high emotional impact and predominantly visual modalities will exhibit differences in the coverage, duration, and occurrence of specific microstates compared to those with low impact or non-visual modalities. The findings would provide insight into the neurodynamic mechanisms underlying visual mental imagery as modulated by sensory modality or emotional engagement, and could inform the development of therapeutic interventions based on guided imagery, positive memory recall, or aesthetic stimulation, with potential applications for emotional regulation and psychological well-being.

Flattened Spectra, Dilated Pupils: Neural Markers Of Cognitive Load

Tomás Bosch Messina[1], Vicente Medel[2], Tomás Ossandón[1]

(1) PUC, Psychiatry, Medicine, Av. General Libertador Bernardo O'Higgins 340, Santiago, Chile
(2) UAI, Psychology, Psychology, Diagonal las Torres 2640, Santiago, Chile

Adaptive attention has been hypothesized to reflect interactions

between locus-coeruleus noradrenergic (LC-NE) arousal and cortical excitation–inhibition balance. We examined this account using high-density EEG (128 channels) and 1 kHz pupillometry while thirty healthy adults (18–35 yr) performed multiple-object tracking with parametrically varied attentional load.

EEG was preprocessed (0.5–40 Hz, down-sampled to 250 Hz, ICA-cleaned) and epoched around the 10 s tracking period. Power spectra were estimated and spectrally parameterized to obtain the aperiodic exponent. Pupil traces were blink-corrected, band-pass filtered (0.05–2.5 Hz), z-scored per trial, and aligned to stimulus onsets.
Repeated-measures analyses indicated significant effects of load on both the aperiodic exponent and mean pupil dilation. Linear mixed-effects models showed that each measure was associated with trial-level accuracy. Cluster-based permutation tests identified load-sensitive EEG clusters after motion onset.
Heavier tracking load was accompanied by larger phasic pupil dilations—consistent with stronger engagement of arousal systems—and by flatter aperiodic exponents. Larger phasic pupil responses were associated with flatter exponents, and trials showing larger changes in both signals tended to have higher accuracy. A model including both predictors explained accuracy better than models including either alone.
These results link pupil-indexed arousal and EEG aperiodic activity to performance during sustained visuospatial attention.

Funding: Fondecyt reluar 1230383

Differential effects of acute administration of three psychedelics on locomotor behavior in Drosophila melanogaster.

Maximiliano Elgueta Reyes[2], Jorge Campusano Astorga[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Ciencias Biológicas, Santiago, Chile
(2) Pontificia Universidad Católica de Chile, Doctorado Interdisciplinario en Neurociencias, Santiago, Chile

Psychedelics are psychoactive agents that induce changes in thought, perception, and mood. Among them, MDMA and psilocybin have shown therapeutic potential by modulating fear extinction and reconsolidation in humans and rodents. On the other hand, ibogaine, a non-classical psychedelic, has been associated with reduced anxiety, antidepressant effects, and decreased drug-seeking behavior. This study aimed to evaluate the behavioral effects of acute MDMA, psilocin, and ibogaine administration in Drosophila melanogaster, to assess the utility of this species as a model for psychedelic research. Material and Methods: Males and female flies aged 3 to 5 days post-eclosion were starved for 16 hours before being exposed to either a control solution (vehicle) or MDMA, psilocin and ibogaine (0.06, 0.125, 0.25, 0.5, or 1 mM) for 90 minutes. Locomotor activity and social behavior were assessed in both individual and group settings. Results: Ibogaine, but not psilocin or MDMA, induced significant reductions in distance traveled and activity time at lower doses. Other locomotor parameters, such as speed and climbing ability, remained unaffected by all three compounds. Social behaviors, including aggregation, were also unchanged by any treatment. Discussion: These findings suggest that ibogaine selectively affects locomotor activity without impairing motor coordination or social interaction. This supports the use of Drosophila melanogaster as a promising model to study specific behavioral effects of psychedelics. Additionally, it contributes to a broader understanding of how these substances may be used to address psychiatric conditions such as addiction, stress-related disorders, depression, and maladaptive fear memories.

Funding: Work funded by Fondecyt Grant n° 1231556 (JMC). ME is supported by ANID Doctoral Fellowship No. 21231956

Differential Effects of Kinesthetic Motor Imagery and Action Observation on the Cortical Dynamics of Semantic Processing of Action Verbs

Javiera Parada[1], Francisco Aboitiz[1], Marcela Perrone[2]

(1) Pontificia Universidad Católica de Chile, Neurociencias, Medicina
(2) Université Grenoble Alpes, Human and Social Sciences, grenoble, France

Neurological conditions such as stroke, Parkinson's disease, and neurodegenerative disorders often impair both motor and language systems, highlighting their functional interdependence. Processing action verbs engages sensorimotor networks even without overt motor execution. Strategies such as kinesthetic motor imagery (KMI) and action observation (AO) can activate these networks through distinct mechanisms: KMI is a voluntary, top-down process, while AO is automatic and perception-driven.

This study compares the effects of short-term KMI and AO training on the lexico-semantic processing of action and abstract verbs, assessed through a semantic decision (SD) task with electroencephalographic (EEG) recording in pre- and post-training phases. Analyses include behavioral measures (reaction time and accuracy) and neurophysiological indices focused on the N400 component amplitude in posterior temporal regions and beta-band (13–30 Hz) power over the premotor cortex.

Preliminary behavioral findings indicate that KMI tends to produce greater post-training improvement in reaction times for action verbs than AO, without compromising accuracy. However, the primary aim is to characterize how each motor simulation modality modulates cortical dynamics associated with motor–semantic integration, providing evidence on whether their effects occur during early stages of lexical–semantic access or later during integrative processing.
By integrating behavioral and neurophysiological evidence, this work seeks to advance our understanding of the mechanisms underlying motor simulation in language and to inform the design of motor-based interventions for language rehabilitation.

Funding: This research was supported by the Beca de Doctorado Nacional (ANID), Chile- Año 2024 (Folio: 21241523)

Getting in the Zone: A Progressive Task Paradigm for Inducing and Characterizing Flow State Dynamics

Sebastian Perez-Gonzalez[1], Rodrigo Henríquez-Ch[3], Maria Rodriguez-Fernandez[2], Francisco Aboitiz[1]

(1) Pontificia Universidad Católica de Chile, Department of Psychiatry, Faculty of Medicine and School of Medicine, Marcoleta 391, Centro de Investigaciones Médicas, Santiago, Chile
(2) Pontificia Universidad Católica de Chile, Institute for Biological and Medical Engineering, Schools of Engineering, Medicine and Biological Sciences, Avda.Vicuña Mackenna 4860, Macul, Santiago, Santiago, Chile
(3) Pontificia Universidad Católica, Departament of Neurology, Faculty of Medicine and School of Medicine, Av. Libertador Bernardo O"Higgins 340, Santiago, Chile

How does the brain achieve its best performance? The Flow State (FS) is a condition of optimal performance characterized by deep immersion, focused attention, and a balance between task demands and individual skills. This state is linked to heightened attention and optimal levels of alertness, which contribute to peak performance. Despite its relevance, FS is often assessed using isolated psychophysical parameters or subjective surveys, with limited integration of performance-based task calibration.
We developed a visual task with progressively adaptive difficulty, tailored to individual performance from a previous training session, to systematically elicit FS. This design defined three difficulty levels: easy, flow-inducing, and challenging —with the aim of identifying trade-offs between accuracy and reaction time (RT).
Seven participants completed the training and performed in all three experimental conditions while RT, hit rates, and FS self-report surveys were recorded. Significant differences were observed between easy and FS, and between easy and challenging conditions. While RT generally declines with increasing difficulty, inter-individual differences suggested possible strategic adaptations. FS survey responses supported the subjective experience of being “in the zone” and feeling their best during the flow-inducing condition.
This pilot study introduces a progressive and individualized task paradigm that enables finer differentiation between performance states. By integrating psychophysical metrics with subjective assessments, this approach lays the groundwork for future studies investigating dynamic changes in attentional network dynamics and the neurophysiological mechanisms underlying FS.

Astrogliosis-Induced Neuroinflammation as a Mechanism of Synaptic Plasticity Impairment in Early Obesity: Regional Expression of GFAP, AMPA, and NMDA Receptors in the Dorsal and Ventral Hippocampus

Melissa Salazar Cea[1,2], Ramón Sotomayor Zárate[2], Jorge Escobar Luna[2,3]

(1) Universidad de Valparaíso, Escuela de Química y Farmacia, Facultad de Farmacia, Avenida Gran Bretaña 1111 Valparaíso, Chile
(2) Universidad de Valparaíso, Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias, Avenida Gran Bretaña 1111, Valparaíso, Chile
(3) Universidad de Valparaíso, Programa de Doctorado en Ciencias Mención Neurociencias, Facultad de Ciencias, Avenida Gran Bretaña 1111, Valparaíso, Chile

Childhood obesity has become a global public health crisis, not only due to its metabolic consequences but also because of its impact on brain function. Accumulating evidence indicates that exposure to high-fat diets (HFD) during early stages of neurodevelopment can induce cognitive alterations, particularly affecting the hippocampus. This vulnerability has been linked to sustained neuroinflammation, characterized by astrocytic activation or astrogliosis, which disrupts the synaptic environment and modifies molecular mechanisms essential for plasticity, such as the transcriptional regulation of glutamatergic receptors.
This study evaluated whether chronic exposure to HFD from weaning (PND 21 to 77) induces astrogliosis and affects the expression of AMPA and NMDA receptor subunits, which are key for spatial memory consolidation. C57BL/6 mice were fed an HFD or a control diet. The expression levels of Gfap, Gria1, Gria2, Grin1, Grin2a, and Grin2b were quantified by RT-qPCR in dorsal and ventral hippocampus. In parallel, spatial memory was assessed using the Y-maze test.
In HFD males, a significant increase in Gfap and all analyzed AMPA and NMDA subunits was observed, indicating astrogliosis and glutamatergic hyperactivity. Moreover, significant differences in spatial behavior were detected, although the small sample size (n = 2–3) limits the robustness of these findings. In contrast, HFD females did not show molecular or behavioral alterations. These results suggest a sex- and region-specific response to early-life obesity, which could precede more evident cognitive impairment at later stages.

Funding: FONDECYT Grant N° 120-0474, Dr. Ramón Sotomayor Zárate, University of Valparaíso.

Behavioral and neurophysiological modulation of inhibitory control in children with adhd: a dynamic trial-to-trial analysis in the go/nogo task

Piedad Maldonado[1], Francisco Aboitiz[1], Francisco Zamorano[1]

(1) Pontificia Universidad Católica de Chile, Facultad de Medicina, Marcoleta 391, Santiago Centro, Chile

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition that impairs self-regulation and goal-directed behavior. One of the most studied cognitive deficits in ADHD is inhibitory control (IC)—the ability to suppress automatic responses in favor of context-appropriate actions. However, few studies have examined how this mechanism dynamically adapts to contextual demands and trial history, particularly in children. This study addressed that gap by performing a trial-by-trial analysis of behavioral and electrophysiological dynamics during a Go/NoGo task in 51 children (28 with ADHD and 23 typically developing, TD), manipulating stimulus presentation speed and cognitive load. Behavioral results showed that children with ADHD exhibited greater reaction time variability and more commission errors, especially under conditions of high

temporal and cognitive demand. In contrast, TD children showed strategic behavioral adjustments, indicative of efficient proactive control. At the neurophysiological level, the TD group demonstrated significant modulation of the P3b component in response to increasing demands, reflecting dynamic allocation of attentional resources. Conversely, the ADHD group showed no such modulation, suggesting a deficit in proactive control mechanisms.
These findings support dual mechanisms of control models and highlight the need for interventions aimed at enhancing contextual adaptation and proactive control strategies in ADHD. Furthermore, P3b modulation emerges as a promising neurophysiological biomarker for evaluating treatment efficacy and monitoring cognitive progress in affected children.
Overall, this study advances our understanding of the neural and behavioral foundations of IC in ADHD, emphasizing the crucial role of context and trial history in shaping inhibitory performance and adaptive control.

Funding: Beca anid doctorado nacional Folio n° 21210625 Beca SCN-IBRO y de la Sociedad Chilena de Neurociencia

Analysis of eye movements and decision-making during the interpretation of ophthalmological examinations at different experience levels.

Sofia Muñoz[1,2], Tomas Miño[1,2], Daniela Castillo[1], Ivan Plaza Rosales[1,2]

(1) Universidad de Chile, Department of Medical Technology, Faculty of Medicine, Av. Independencia 1027, Independencia, Región Metropolitana, Santiago, Chile
(2) Universidad de Chile, Laboratorio de Neurosistemas, Department of Neurosciences, Faculty of Medicine, Av. Independencia 1027, Independencia, Región Metropolitana, Santiago, Chile

Abstract:
Background: Early diagnosis of eye diseases like glaucoma depends on accurate interpretation of visual examinations such as optical coherence tomography (OCT) and computerized visual field testing (CVT). A correct diagnosis is associated with cognitive processes acquired through experience and reflected in the examiner's eye behavior. Currently, the differences in visual examination patterns (such as fixations, saccades, and regions of interest (ROIs)) between students in training and professionals and their relationship to diagnostic efficacy are unknown. We hypothesize that as experience increases, eye movement patterns become more efficient and localized, with longer fixation times and longer saccades toward regions of interest, thereby increasing diagnostic accuracy.

Methods: In this study, we had 24 subjects grouped according to their level of experience in ophthalmology in three groups: 4th- and 5th-year students and qualified professionals in Medical Technology. Eye movements were recorded during the observation and diagnosis of OCT and CVC examinations using eye tracking (EyeLink 1000). Variables such as the number and duration of fixations and saccades were analyzed, in addition to ROIs, along with reaction times, accuracy, and confidence levels.

Results: The results revealed significant differences between groups, with professionals focusing on key areas, demonstrating greater diagnostic accuracy, shorter response times, and more efficient search strategies.

Conclusions: Clinical experience modulates visual patterns while interpreting ophthalmological examinations, suggesting that eye movements may be objective indicators of expertise.

Maternal exposure to witnessed social defeat stress during lactation induces sex-specific disruptions in juvenile social play behavior

Andrew Justin Taylor[1], Robinson Carrasco Gutiérrez[1], Arabia Olea Araya[1], Pablo R Moya[2], Alexies Dagnino Subiare[1,3]

(1) Laboratory of Stress Neurobiology, Interdisciplinary Centre for Health Studies (CIESAL), Institute of Physiology, Faculty of Science, Universidad de Valparaiso, Valparaiso, Chile
(2) Laboratory of Neurogenetics, Centro de Estudios Traslacionales en Estrés y Salud Mental (C-ESTRES),, Institute of Physiology, Faculty of Science, Universidad de Valparaiso, Valparaiso, Chile
(3) Millennium Institute for Depression and Personality Research (MIDAP), Vicuña Mackenna Avenue 4860, Santiago, Chile

Maternal stress during lactation could impair offspring neurodevelopment, impacting behavioral and physiological outcomes. However, the mechanisms by which maternal exposure to observational aggression affect early life social play and stress physiology of offspring, remain poorly understood.

Witness social defeat stress (WSS) is a model of observable social aggression in which a third-party rodent observes the aggressive supine pinning (social defeat) of an intruder by a resident, generating robust physiological and behavioral effects in observers.

We developed a novel early-life stress (ELS) model using maternal exposure to WSS during lactation and assessed its effects on early juvenile offspring. At postnatal day 24, same-sex, age-matched offspring—previously isolated for 12 hours—were paired to evaluate social play behavior via manual scoring of pouncing, pinning, chasing, and evading. In addition, adrenal cortex weight was measured to assess stress physiology.
WSS-exposed juvenile males showed significantly reduced pouncing and increased adrenal cortex weight compared to controls, while females exhibited no significant differences.

These findings reveal sex-specific alterations in behavior and physiology following maternal exposure to WSS. This model highlights a novel pathway by which maternal social stress during lactation can program sex-specific outcomes, with relevance to understanding social deficits in neuropsychiatric disorders.

Funding: Proyecto Puente-UV Nº UVA20993, CUECH RED21993, FONDECYT 1231012

Fenofibrate treatment during withdrawal reverses symptoms of ethanol-induced depression in male rats

Marcelo León Olivares[1], Eduardo Karahanian[1], Diliana Perez-Reyton[1], Camila Vasquez-Ulloa[1], Lucas Marambio-Ruiz[1]

(1) Institute of Biomedical Sciences, Faculty of Health Sciences, Universidad Autónoma de Chile

Alcohol use disorder (AUD) and major depression frequently co-occur, both involving significant neuroinflammatory components. Current treatments are often ineffective in addressing AUD-related depression, highlighting the need for novel therapeutic approaches. Previous studies showed that fenofibrate, a peroxisome proliferator-activated receptor alpha (PPAR-α) agonist, reduces voluntary alcohol intake and attenuates neuroinflammation and oxidative stress in alcohol-preferring rats. This study investigated whether fenofibrate administered during alcohol withdrawal could alleviate ethanol-induced depressive symptoms and neurobiological alterations.
Male rats received ethanol (1 g/kg, i.p.) on alternate days for three weeks; controls received saline. During a two-week withdrawal period, half of the ethanol-treated rats received fenofibrate (50 mg/kg/day) for the final five days. Behavioral assessments included the open field, tail suspension, and sucrose intake tests. RT-qPCR evaluated proinflammatory cytokine and brain-derived neurotrophic factor (BDNF) expression in the prefrontal cortex (PFC) and hippocampus, while Golgi staining assessed dendritic arborization.
Ethanol exposure increased anxiety and immobility in behavioral tests, consistent with depressive-like behaviors, and elevated TNF-α, IL-1β, and IL-6 levels. Fenofibrate reversed these behavioral and molecular effects, normalized PFC BDNF expression, and partially restored dendritic complexity. However, ethanol-induced reductions in sucrose intake after withdrawal—reflecting anhedonia—were not reversed by fenofibrate.
These findings suggest that fenofibrate mitigates ethanol-induced depressive-like behaviors and neurobiological dysfunctions through anti-inflammatory and neuroprotective mechanisms. Given its established clinical use and safety profile as an FDA-approved drug, fenofibrate shows promise as a translational therapeutic adjunct for treating depression in individuals with AUD.

Funding: ANILLO ANID ACT210012 (to EK), Fondecyt 11240442 (to DPR)

Connexin 36 in the Female Medial Amygdala: Implications for Anxiety-Related Behavior

Andrea Fierro Ortiz[1], Montserrat Oyarzún[1], Adolfo Agurto[1], Sergio López[1], Karina Oyarce[2], Roberto Elizondo-Vega[1], Antonia Recabal-Beyer[1]

(1) Universidad de Concepción, Departamento de Biología Celular, Facultad de Ciencias Biológicas, Concepción, Chile
(2) Universidad San Sebastián, Facultad de Medicina y Ciencia, Concepción, Chile

Anxiety disorders are highly prevalent worldwide and are among the leading causes of disability. These disorders are influenced by biological, environmental, and psychological factors and are closely linked to the central nervous system (CNS). Within the CNS, the medial amygdala (MeA) plays a key role in processing emotional and social stimuli, such as fear and reward, and in generating appropriate behavioral responses. Notably, the MeA shows sex-specific differences in both size and connectivity. Recent findings from our lab reveal that the MeA contains a high density of electrical synapses—specialized connections between neurons formed by gap junctions, primarily composed of connexin 36 (Cx36). These synapses allow the direct passage of ions and small molecules, synchronizing neuronal activity and enhancing network excitability. Given this, we investigated how Cx36 expression in the MeA differs between male and female mice, how it is affected by social stress, and how it relates to anxiety-like behaviors. Using immunohistochemistry and qRT-PCR, we measured Cx36 levels in female mice subjected to 8 weeks of social isolation stress. We also tested the effects of bilaterally inhibiting Cx36 in the MeA using an adeno-associated virus. Our results show that Cx36 is expressed in a sex-dependent manner in the MeA, that its expression decreases after social stress, and that its inhibition reduces anxiety-like behavior in female mice. A deeper understanding of the molecular and neural mechanisms of anxiety could offer new insights into its biological basis and guide the development of more effective treatments.

Funding : FONDECYT INICIO 11240516

Chewing as a Bottom-Up Neuromodulator of Cortical Dynamics: Electrophysiological Evidence from EEG Studies

Sebastian Espinoza Espinoza[1], Wael El-Deredy[2]

(1) Universidad de Valparaíso, Dentistry, Dentistry, Subida Leopoldo Carvallo 211, VALPARAISO, Chile
(2) Universidad de Valparaiso, School of Biomedical Engineering, Faculty of Engeniering, General Cruz 222, Valparaiso, Chile

Chewing has been proposed as a modulator of cognitive function, yet the neural mechanisms through which it influences cortical activity remain poorly defined. We conducted two independent EEG experiments to investigate how rhythmic mastication modulates oscillatory brain dynamics and cognitive performance during a visuospatial 2-back working memory task. The first experiment assessed real-time effects by recording EEG while participants performed the task while chewing and compared to a no-chewing control block; chewing significantly improved behavioral performance, with a 13.4% reduction in reaction time.

EEG analyses revealed a selective increase in frontocentral theta power (4–7 Hz) during the late post-stimulus window (900–1300 ms), which negatively correlated with inverse efficiency scores ($\rho = -0.36$, $p = 0.0216$), indicating enhanced cognitive efficiency. Additionally, theta amplitude positively correlated with chewing frequency ($\rho = 0.32$, $p = 0.0376$), and robust phase–amplitude coupling (PAC) was observed between the chewing rhythm (0.5–2 Hz) and theta amplitude ($p < 0.0001$), suggesting real-time cortical entrainment.

In the second experiment, chewing occurred one minute before the task to assess sustained effects. Results showed increased frontocentral theta power, enhanced frontoparietal functional connectivity measured via Phase Lag Index (PLI), and improved inverse efficiency scores. These neural changes were also correlated with chewing frequency, reinforcing a dose–dependent effect.
Together, the findings demonstrate that chewing modulates brain function both during and after mastication, through real-time entrainment and sustained neuromodulatory effects, offering a mechanistic basis for the cognitive benefits of rhythmic sensorimotor activity.

Funding: Beca Doctorado Nacional. ANID, Chile. Grant number 21220968Fondecyt Regular. PROYECTO N° 1241695

Morphological analysis of the Drosophila melanogaster blood-brain barrier after penetrating traumatic brain injury

Jennifer Salazar-Tirado[1], Esteban Contreras-Sepúlveda[1]

(1) Universidad de Concepción, Departamento de Biología Celular, Facultad de Ciencias Biológicas, Barrio Universitario s/n Concepción, Concepción, Chile

The blood-brain barrier (BBB) is a structure that protects and maintains the homeostasis of the nervous system through its selective permeability, which can be compromised by trauma, stroke, and other conditions. Although the BBB has been reported to possess regenerative capacity, the molecular mechanisms underlying this process remain incompletely understood. Drosophila melanogaster has a BBB with functions and characteristics similar to the human counterpart, making it a suitable model for studying BBB damage and repair. In this study, a mechanical strategy—penetrating traumatic brain injury (pTBI)—was used to standardize a protocol for BBB injury induction and regeneration analysis. Immunofluorescence analysis revealed that pTBI-induced damage is resolved 24 hours post-injury. Notably, there was an increase in actin localization and in the membrane density of the glial cells that form the BBB at the injury site, suggesting a structural restoration process of the barrier.

Funding: ANID-Subdirección de Capital Humano/Doctorado Nacional/2025/Folio 21251072

Neural stem cells grafting: a new approach to improve neurological functions in the hydrocephalic HTx rat, a murine model of congenital hydrocephalus

Vicente Romero[1], Fabián López[1], Sebastián Guerrero[1], Rosa Muñoz[1], Karin Vio[1], Montserrat Guerra[1]

(1) Universidad Austral de Chile, Instituto de Anatomía, Histología y Patología, Facultad de Medicina, Valdivia, Chile

Introduction Congenital hydrocephalus is a condition present at birth in which excess cerebrospinal fluid (CSF) collects within the brain. It leads to neural and cognitive impairment which are irreparable with currently CSF-derivative treatments. Hydrocephalus and neurological outcomes share a common pathway: a cell-junction pathology of neural stem cells/ependyma that lines the embryonic ventricular zone. Goal. To explore a stem cell therapy as a potential approach to improve neural functions in the hydrocephalic brain. Methods Neural stem cells were isolated and grown as neurospheres to be further grafted into the brain of hydrocephalic HTx rats (n=4) at postnatal day 7 (PN7). Three weeks after grafting, neural and cognitive functions were assessed by using standarized tests (NOR test). Non hydrocephalic HTx rats, hydrocephalic HTx rats without treatment and shunt HTx rats, n=4 for each group, were also studied. Results and Discussion Neural stem cells grafting extended lifespan of grafted animals and significantly improved specific neural functions, such as sensory and motor functions, and equilibrium. However, hydrocephalus and cognitive functions were not improved in the period of experimentation. Overall, these findings open an avenue for the use of stem cells to improve quality of life of children born with hydrocephalus. New experiments to study the long-term outcomes and mechanism of action of grafted cells are in progress. Stem cells labeling by using a viral-vector fluorescent will let study the differentiation, commitment and determination of stem cells after grafting in the hydrocephalic brain. *Romero and Lopez both qualify as first authors

Funding: MUJ-INV-2023-03 (UACh).

Improved regeneration of the neuromuscular synapse upon canonical Wnt pathway inhibition

Francisca Bermedo García[1], Jessica Mella[1], Viviana Perez[1], Lucía Tabares[2], Juan Pablo Henríquez[1]

(1) Neuromuscular Studies Laboratory (NeSt Lab), Universidad Austral de Chile, Instituto de Anatomía, Histología y Patología, Facultad de Medicina, Valdivia, Chile
(2) Universidad de Sevilla, Facultad de Medicina, Sevilla, España

Introduction: The neuromuscular junction (NMJ) is a peripheral synapse formed by a motor axon terminal, a muscle fiber domain, and terminal Schwann cells (tSCs). Several conditions affecting NMJ integrity correlate with augmented activity of canonical Wnt signaling, but the functional consequences of this activation on NMJ regeneration are unknown. Here, we studied the effect of pharmacological modulation of canonical Wnt signaling on nerve injury-dependent NMJ regeneration.
Material and methods: We used subcutaneous injections of Andrographolide and XAV-939 to activate or inhibit Wnt signaling, respectively, in adult mice (3-6 m.o.; n=3/group). At different days post injury (dpi), the cranial Levator auris longus (LAL) muscles were dissected and stained to determine NMJ morphology through confocal microscopy or ultrastructure through transmission electron microscopy (TEM). Neurotransmission was evaluated by intracellular recording of ex vivo LAL muscle preparations.
Results: Canonical Wnt pathway activation resulted in a reduced proportion of postsynaptic domains contacted by regenerated motor axons 7 dpi, and a decrease in axon diameter 15 dpi. Consistently, electrophysiological assays showed impaired amplitude of evoked end-plate potentials

(EPP) and quantal content (QC) at 21 dpi. Remarkably, pharmacological inhibition of canonical Wnt signaling resulted in increased axonal diameter and EPP amplitude at 21 dpi.The pharmacological treatments had no effects on the gross morphology of the postsynaptic domains. These results suggest that the inhibition of the canonical Wnt pathway improves the functional recovery of the NMJ.
Discussion: Our findings open promising therapeutic prospects for NMJ repair through canonical Wnt pathway modulation.

Funding: Funded by FONDECYT 1221213 to JPH

Changes in cortical activity after an intensive motor skill learning intervention in children with bilateral cerebral palsy

Natalia Perez Ramirez[1,2], Daniela Ebner-Karestinos[2], Rodrigo Araneda[2]

(1) Universidad Andrés Bello, Exercise and Rehabilitation Sciences Institute - Rehabilitation Sciences Doctorate Program, Faculty of Rehabilitation Science, Fernandez Concha 700, Las Condes, Santiago, Chile
(2) Universidad Andrés Bello, Exercise and Rehabilitation Sciences Institute - School of Physical Therapy, Faculty of Rehabilitation Science, Fernandez Concha 700, Las Condes, Santiago, Chile

Background
Cerebral palsy (CP) is a childhood-onset, non-progressive disorder affecting posture and movement. Hand–Arm Bimanual Intensive Therapy Including Lower Extremities (HABIT-ILE) is an intensive motor intervention shown to induce fronto-parietal network activation changes in unilateral spastic CP. Its capacity to promote neuroplastic changes in bilateral CP (bCP) remains unclear. This study examined cortical activity changes in children with bCP following HABIT-ILE intervention.

Methods
Ten children with bCP, classified with mild-to-moderate gross motor function and manual ability, participated in a 10-day HABIT-ILE intervention between December 2024 and January 2025. Cortical activity was measured before and after HABIT-ILE using fNIRS (Brite MKIII, Artinis Medical Systems, The Netherlands), with optodes placed over bilateral frontal and motor cortices during a unilateral manipulation task. Non-parametric analyses examined changes in oxyhaemoglobin and deoxyhaemoglobin concentrations, quantifying differences in the haemodynamic response function. Due to variability in gross motor function and manual ability statistical analyses were performed individually.

Results
Significant changes were observed post-intervention ($p < 0.05$), highlighting the role of frontal and motor cortices in motor skill acquisition and execution.

Conclusions
These preliminary findings suggest that HABIT-ILE can change cortical activity in children with bilateral CP, supporting its role as a motor learning–based therapy capable of driving neuroplastic changes. These results contribute to the growing evidence base for intensive motor interventions in this population.

Funding: Concurso de iniciación a la investigación (DI-07-24/INI) of Universidad Andrés Bello and National Research and Development Agency (ANID) of Chile, Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT, ANID Chile), grant number 11250472.

Detection and optogenetic control of epileptic seizures based on neural dynamics

Ignacio Negrón-Oyarzo[1], Lopez-Quilodran Nélida[1,2], Joaquin Mendoza[1,3], Francisca García[1], Astrid Muñoz-Pérez de Arce[1,2], Lorena Chacana-Véliz[1,2], Nelson Espinosa[4]

(1) Laboratorio de Neurofisiología Cognitiva, Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile.
(2) Doctorado en Ciencias, mención en Neurociencias, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile.
(3) Magister en Ciencias de la Ingeniería mención en Ingeniería Biomédica, Facultad de Ingeniería, Universidad de Valparaíso, Valparaíso, Chile.
(4) Centro Integrativo de Neurociencias and Departamento de Psiquiatría, Pontificia Universidad Católica de Chile, Santiago, Chile.

The anticipated detection and modulation of epileptic seizures has been a major goal in neuroscience research. Nevertheless, achieving these results has been significantly challenging. Here we applied an alternative approach based on the variable temporal structure of neural activity (i.e., dynamics). In the first experiment, we recorded the local field potential (LFP) from the neocortex and hippocampus (HPC) during seizures from an in vivo freely moving rodent model of chronic epilepsy, and we evaluated the neural dynamics of seizures. In the second experiment, we applied optogenetic stimulation during seizures of an epileptic channelrhodopsin (ChR2)-expressing mice to modulate neural activity dynamics.

Through the analysis of non-linear features of the LFP, we found that measurements of neural dynamics changed significantly during the different stages of epileptic seizures (interictal, preictal, ictal, and postictal), allowing the accurate stage identification. A deeper and more detailed analysis revealed gradual alterations of neural dynamics around the transition between stages, allowing the anticipated detection of stage transitions. The implementation of these analytical tools in real time allowed the accurate detection of seizures. On the other hand, through the specific expression of the ChR2 in hippocampal pyramidal neurons, we implemented an optogenetic stimulation protocol that does not alter neural dynamics. Preliminary experiments showed that, when applied to an epileptic rodent model, this stimulation protocol was able to delay the occurrence of epileptic seizures. These findings provide a valuable approach for accurate control of epilepsy.

Funding: FONDECYT Iniciación N°11160251; ANID; Proyecto Ciencia+ 2025: "Potenciando la innovación desde la ciencia" enmarcado en el proyecto Ciencia 2030", Vicerrectoría de Investigación, Universidad de Valparaíso.

Eaat3 overexpression confers resilience to chronic stress: behavioral studies and redox state in mice model

Wladimir Plaza-Briceño[2,4], Paula Acevedo-Hernández[2], Ramón Sotomayor-Zárate[2,3], Pablo Moya[1,2]

(1) Centro de Estudios Traslacionales en Estrés y Salud Mental (C-ESTRES), Universidad de Valparaíso., Valparaíso, Chile
(2) Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile
(3) Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Universidad de Valparaíso, Valparaíso, Chile
(4) Programa de Doctorado en Ciencias mención Neurociencia, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile

Depression is a debilitating mood disorder whose etiology remains unclear. Recent research has linked depression to both oxidative stress and glutamate dysfunction. Studies in animal stress models and humans show decreased antioxidant activity and increased oxidizing agents. The glutamatergic hypothesis suggests that depression pathophysiology involves glutamate imbalance. Neuronal EAAT3 not only controls glutamate spillover but also transports cysteine, a precursor necessary for glutathione (GSH) synthesis. Studies have demonstrated a regulatory effect of EAAT3 on GSH levels: EAAT3 knockout animals show decreased GSH levels, while EAAT3 overexpression (OE) leads to elevated GSH levels. These findings suggest that EAAT3 plays a neuroprotective role against oxidative stress. Our aim was to determine if EAAT3 OE is a protective factor against oxidative stress and the manifestation of a depressive phenotype induced by unpredictable chronic mild stress (UCMS). We used transgenic mice overexpressing EAAT3 under CaMKIIa promoter. Mice were evaluated under basal and stress conditions using behavioral tests, and oxidative stress markers (malondialdehyde MDA, nitric oxide and GSH) were measured in prefrontal cortex, hippocampus and striatum. Results showed that EAAT3 OE confers resilience to chronic stress. Nevertheless, MDA levels remained unchanged in prefrontal cortex, hippocampus and striatum. In the other hand, we observed a basal reductor state in OE but chronic stress diminished this status in hippocampus. Our results suggest future evaluation of GSH in prefrontal cortex and striatum, and glutamate levels using additional methods.

Funding: FONDECYT 1231012, Beca Doctorado Nacional ANID N°21220829

Loss of sensitivity to Propofol in the 5xFAD mouse model of Alzheimer's disease: role of microglia and GABA(A) receptors in the hippocampus.

Pedro Lobos[1], Jamileth More[1], Bárbara Bruna[1], Benjamín Césped[2], Roberto Calderón[2], Rodrigo Gutiérrez Rojas[1,3], José Ignacio Egaña Tomic[1,3], Antonello Penna Silva[1,3]

(1) Universidad de Chile, Centro de Investigación Clínica Avanzada (CICA), Facultad de Medicina y Hospital Clínico, Dr. Carlos Lorca Tobar 999, 3er piso, sector A. Independencia, Santiago, Chile
(2) Universidad de Chile, Escuela de Medicina, Facultad de Medicina, Av. Independencia 1027, Santiago, Chile
(3) Universidad de Chile, Anestesiología y Medicina Perioperatoria, Facultad de Medicina, Dr. Carlos Lorca Tobar 999, 2° piso, sector B. Independencia, Santiago, Chile

Alzheimer's disease (AD) presents with an excitatory/inhibitory (E/I) imbalance that evolves with disease progression. This study evaluated whether sensitivity to the GABAergic anesthetic propofol changes depending on disease stage in the 5xFAD mouse model.
Anesthesia was induced with propofol in 5xFAD and control mice at 6 (early stage) and 18 months (late stage), measuring the righting reflex recovery time (RORR). Hippocampal expression of the transcription factor Npas4 and microglial activation were analyzed.
The results reveal a biphasic pattern. At 6 months, 5xFAD mice showed faster RORR recovery ($p < 0.05$), indicating anesthetic hyposensitivity. In contrast, at 18 months, they showed a prolonged recovery ($p < 0.05$), reflecting hypersensitivity. At the molecular level, the early stage was associated with a significant reduction in Npas4, a key regulator of inhibitory synapses, and with proinflammatory microglial morphology.
We conclude that sensitivity to GABAergic drugs in the 5xFAD model changes dramatically with disease progression, shifting from initial resistance to late vulnerability. This pathological plasticity, possibly mediated by Npas4 dysregulation and neuroinflammation, underscores the importance of considering disease stage in the anesthetic management of patients with AD.

Funding: FONDEF ID21I10193

Sex-dependent alterations in thyroid hormone production, brain entry, and metabolism in the 5XFAD mouse model of Alzheimer's disease

Elizabeth Leiva Pastén[1,2,3], Ana Montero Pedrazuela[5], Camila Escobar Infante[2,4], Mario Párraga San Román[2,4], Ana Guadaño Ferraz[5], Soledad Bárez López[5], Daniela López Espíndola[1,2]

(1) Universidad de Valparaíso, Escuela de Tecnología Médica, Facultad de Medicina, Angamos 655, Reñaca, Viña del Mar, Chile
(2) Universidad de Valparaíso, Centro Interdisciplinario de Investigación Biomédica e Ingeniería para la salud MEDING, Facultad de Medicina, Angamos 650, Reñaca, Viña del Mar, Chile
(3) Universidad de Valparaíso, Programa de Magíster en Ciencias Biológicas mención Neurociencia, Facultad de Ciencias, Av. Gran Bretaña 1111 Playa Ancha, Valparaíso, Chile
(4) Universidad de Valparaíso, Escuela de Medicina, Facultad de Medicina, Angamos 655, Reñaca, Viña del Mar, Chile
(5) Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas (CSIC)-Universidad Autónoma de Madrid (UAM), Department of Endocrine and Nervous System Pathophysiology, Arturo Duperier 4, 28029, Madrid, Spain

Introduction: Multiple mechanisms are currently being investigated as contributors to Alzheimer's disease (AD) pathophysiology, including potential alterations in thyroid hormones (TH), which regulate key genes involved in the

disease. Changes in T3 and T4 levels have been reported in AD patients; however, the evidence remains contradictory, and sex differences and underlying mechanisms are poorly explored. This study characterizes TH levels, production, brain entry, and metabolism in female and male 5XFAD mice.

Methods: 5XFAD and WT mice were used (n=32, 7 months, both sexes). T3 and T4 levels were measured in plasma, cerebral cortex, and hippocampus by radioimmunoassay. TH production was assessed through morphometric analysis of pituitary and thyroid glands, and immunohistochemistry for TSH (pituitary), and thyroglobulin, PAX-8, and TTF-1 (thyroid). TH entry into the brain was evaluated by immunohistochemistry for the MCT8 transporter in cortical blood vessels and choroid plexus of the fourth ventricle. Finally, TH metabolism was analyzed via RT-qPCR of Dio2 and Dio3 mRNA in cortex and hippocampus.

Results: Female 5XFAD mice preserved hormone availability, despite reduced thyroid functional activity. In contrast, male 5XFAD mice showed lower plasma TH levels and increased thyroid activity. MCT8 expression was altered only in male 5XFAD mice, with increased levels in cortical vessels and decreased levels in the choroid plexus. Dio2 expression remained unchanged; however, Dio3 was decreased in the hippocampus of female 5XFAD mice and increased in 5XFAD males.
These results suggest sex- and region-specific alterations in TH production, entry, and metabolism in the context of AD.

Funding: This work was supported by the chilean government through Fondo Nacional de Desarrollo Científico y Tecnológico FONDECYT (#11230727 to D.L.-E).

Differential regulation of T3 signaling in the cerebral cortex and hippocampus of a transgenic Alzheimer's disease model

Daniela González Pizarro[2,3], Camila Escobar Infante[2,5], Ana Montero Pedrazuela[4], Mario Párraga San Román[2,5], Ana Guadaño Ferraz[4], Soledad Bárez López[4], Daniela López Espíndola[1,2]

(1) Universidad de Valparaíso, Escuela de Tecnología Médica, Facultad de Medicina, Angamos 655, Reñaca, Viña del Mar, Chile
(2) Universidad de Valparaíso, Centro Interdisciplinario de Investigación Biomédica e Ingeniería para la salud MEDING, Facultad de Medicina, Angamos 650, Reñaca, Viña del Mar, Chile
(3) Universidad de Valparaíso, Programa de Magíster en Ciencias Médicas, mención Biología Celular y Molecular, Facultad de Medicina, Angamos 650,, Reñaca, Viña del Mar, Chile
(4) Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas (CSIC)-Universidad Autónoma de Madrid (UAM), Department of Endocrine and Nervous System Pathophysiology, Arturo Duperier 4, 28029, Madrid, Spain
(5) Universidad de Valparaíso, Escuela de Medicina, Facultad de Medicina, Angamos 655, Reñaca, Viña del Mar, Chile

Thyroid hormones (TH), triiodothyronine (T3) and thyroxine (T4), regulate the expression of genes essential for central nervous system function through binding to nuclear receptors TRα and TRβ. Several studies have linked thyroid dysfunction to neurodegenerative diseases, including Alzheimer's disease (AD), in which dysregulation of TH levels has been reported. Moreover, T3 regulates genes directly involved in the pathogenesis of this disorder.
In this study, we assessed thyroid signaling in the transgenic 5XFAD mouse model, compared with wild-type (WT) controls, considering sex- and brain region–specific differences. Plasma, cortical, and hippocampal levels of T3 and T4 were quantified by radioimmunoassay in male and female mice aged 7 months (n=32). Expression of T3-responsive target genes, as well as TRα and TRβ receptors, was analyzed by RT-qPCR.
Male 5XFAD mice exhibited a significant reduction in plasma T3 and T4. In females, plasma hormone levels were comparable to WT, with only a slight decrease. However, TH levels in cortex and hippocampus remained within the normal range in both sexes.
At the transcriptional level, Mamdc2 (a T3-repressed gene) was overexpressed in both cortex and hippocampus in males and females. In male 5XFAD mice, Hr (a gene strongly activated by T3) was downregulated. Additionally, female 5XFAD mice showed differential regulation of receptors, with increased TRα in the cortex and decreased TRβ in the hippocampus; conversely, in males, TRβ was upregulated in the hippocampus.
These findings suggest altered effective T3 signaling in the 5XFAD model, with sex- and region-specific effects, reinforcing the role of TH in AD pathophysiology.

Role of Glial Lazarillo and LRP1/2 receptors in the accumulation of amyloid beta peptide in a Drosophila melanogaster model of Alzheimer's disease

Cristóbal Apileo[1], Sofía Paredes[2], Esteban Contreras Sepúlveda[1]

(1) Universidad de Concepción, Department of Cell Biology, Faculty of Biological Sciences, Concepción, Chile
(2) Universidad Andrés Bello, Viña del Mar, Chile

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and the accumulation of amyloid-beta (Aβ) peptides in the brain. While the precise mechanisms behind Aβ accumulation remain unclear, impaired clearance is recognized as a contributing factor. One of the Aβ elimination routes involves transport across the blood-brain barrier (BBB), which expresses Low-density Lipoprotein Receptor-Related Protein 1 (LRP1) and Low-density Lipoprotein Receptor-Related Protein 2 (LRP2) that mediate lipid metabolism and facilitate Aβ peptide bound to apolipoprotein E (ApoE). ApoE has different alleles, where ApoE4 is associated with severe AD. For studying Aβ accumulation, we can use Drosophila melanogaster as an animal model, due to its conservated structures with to mammals, including the BBB, LRP receptors and the presence of an ApoE ortholog, Glial Lazarillo (Glaz). However, the BBB clearance route of Aβ has not been studied in this model. In this project, we postulate that the Aβ clearance through the blood-brain barrier is mediated by GLaz lipoprotein and LRP1 and LRP2 receptors. To test this hypothesis, transgenics flies expressing human $A\beta_{1-42}$ peptide and LRP1/2 RNAi or Glaz RNAi were used.

We analyzed the accumulation of $A\beta_{1-42}$ plaques by immunofluorescence and confocal microscopy. Additionally, the neurodegenerative consequences of this $A\beta_{1-42}$ accumulation were evaluated by behavioral and locomotor tests. We expect that reduced expression of LRP1/2 or Glaz will lead to increased Aβ accumulation and exacerbated behavioral deficits, supporting a conserved mechanism of Aβ clearance across species.

Funding: FONDECYT de Iniciación 11230539

Changes in LSD1 isoforms as a mechanism for the establishment of compulsive behavior in an OCD model

Pilar Aguilera Maturana[1], Bastián Rivera Puebla[1], María Estela Andrés Coke[1]

(1) Pontificia Universidad Católica de Chile, Faculty of Biological Sciences, Av. Libertador O´Higgins 340, Santiago, Chile

Compulsive behavior consists in repetitive acts that an individual feels compelled to perform despite being aware that such acts comprise negative consequences. These behaviors are central to several psychiatric disorders, including obsessive-compulsive disorder (OCD) and addiction. A well-characterized animal model used to study this phenomenon is the one described by Szechtman et al. (1998), in which compulsive checking behavior is induced through repeated administration of the selective D2/D3 dopamine receptor agonist, Quinpirole (QNP). A wide range of neurochemical and behavioral aspects of compulsiveness have been described in this model. Nonetheless, the molecular basis by which dopaminergic dysregulation contributes to compulsive behavior development remains unclear. Lysine Specific Demethylase 1 (LSD1) is an enzyme that demethylates H3K4me1/2 epigenetic mark, acting as a transcriptional corepressor. LSD1 has two main isoforms resulting from alternative splicing, a neuron-specific variant (nLSD1) which retains a 12-bp mini-exon (E8a), important for neuronal plasticity, and a ubiquitously expressed isoform (uLSD1). Notably, nLSD1 exhibits diminished transcriptional repressor activity, pointing to a relevant role for uLSD1/nLSD1 variations in the transition between transcriptionally repressed and active states. In line with this, it has been observed that uLSD1/nLSD1 ratio changes in response to QNP treatment within the mesolimbic system, suggesting a mechanism that contributes to the establishment of neuronal response observed in this OCD animal model's dopaminergic neurons, underpinning the development of compulsive behavior.

Funding: PUENTE-2025-9 UC

The Forgotten Sex: Social and Anatomical Characterization of Female Fmr1 KO Mice, a Model of Fragile X Syndrome and Autism

Laura Ocqueteau[1], Alexandra Saavedra[1], Marcela Navarrete M.[1], Felipe Avello[1], Alexia Nuñez-Parra[1], Jorge Mpodozis[1]

(1) Universidad de Chile, Departamento de Biología, Facultad de Ciencias, Las Palmeras 3425, Santiago, Chile

Fragile X syndrome (FXS) is caused by the silencing of the FMR1 gene, located on the X chromosome. Individuals with FXS typically exhibit intellectual disabilities and behavioral traits associated with autism spectrum disorder. Because the condition is X-linked, it occurs more frequently in males than in females, leading most scientific research to focus primarily on male subjects. As a result, relatively little is known about how FXS manifests in females. In this study, we examined social behavior and anatomical features of the accessory olfactory bulb (AOB) in female Fmr1 knockout (KO) mice, a widely used animal model of FXS. We focused on the AOB because it serves as the first processing stage of the vomeronasal system, which is crucial for detecting social olfactory cues and regulating social and sexual behaviors in mice. Similar to male Fmr1 KO mice, female KOs displayed atypical social behaviors, including altered social novelty preference. However, unlike males, female Fmr1 KO mice did not exhibit anatomical changes in the AOB when compared to wild-type controls. These findings provide new insights into the neurobiological mechanisms underlying FXS and autism in females.

mGluR-mediated intracellular calcium dynamics during early postnatal development in a mice model of Fragile X Syndrome

Vania Murga[1], Elias Leiva Salcedo[2], Christian Cea Del Rio[1]

(1) Universidad de Santiago de Chile, Centro de Investigación Biomédica y Aplicada (CIBAP), Escuela de Medicina, Facultad de Ciencias Medicas
(2) Universidad de Santiago de Chile, Departamento de Biología, Facultad de Química y Biología

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and autism spectrum disorder. A well-established hallmark of FXS is the dysregulation of metabotropic glutamate receptor type I (mGluR I)-mediated synaptic plasticity at both excitatory and inhibitory synapses. However, how the downstream signaling cascade of mGluR activation is altered at the level of intracellular calcium remains unclear. Since calcium is a central second messenger that governs both short- and long-term synaptic modifications, we hypothesized that mGluR-mediated Ca^{2+} signaling is disrupted in a murine model of FXS, shaping the synaptic phenotype observed in adulthood. To test this, we combined immunofluorescence and calcium imaging approaches to examine how mGluR1/5 activation influences calcium levels and dynamics during early postnatal development in Fmr1 KO mice. Our results reveal that calcium dynamics are profoundly altered in Fmr1 KO mice, displaying distinct developmental trajectories during early postnatal stages ($p = 0.018$). Specifically, at postnatal day 10 (P10), Fmr1 KO neurons showed reduced maximal evoked fluorescence (F_{MAX}/F_0; 1.40 ± 0.06, n = 20) compared with WT neurons (2.69 ± 0.31, n = 46; $p = 0.021$). By contrast, at P21, Fmr1 KO neurons exhibited significantly higher F_{MAX}/F_0 values than WT (KO = 1.95 ± 0.15 vs. WT = 1.25 ± 0.05; $p = 0.0002$). Together, these findings suggest that early alterations in mGluR-mediated Ca^{2+} signaling may shift the balance of synaptic plasticity in Fmr1 KO mice. This supports the idea that calcium dysregulation underlies the synaptic phenotypes observed in the adult FXS mouse model.

Funding: DICYT 022401CDR

Blood-brain barrier dysfunction increases neurodegeneration in a Drosophila melanogaster Alzheimer´s disease model

Víctor Morales[1], Matías Valderrama[1], Sofía Paredes[1], Javiera Allup[1], Cristobal Apileo[1], Esteban Contreras[1]

(1) Universidad de Concepción, Departamento de Biología Celular, Facultad de Ciencias Biológicas, Edmundo Larenas 219, Concepción, Chile

Alzheimer's disease (AD) is the most common form of dementia worldwide, characterized by the accumulation of insoluble amyloid-beta (Aβ) peptide in the brain, which triggers neurodegeneration, memory loss, and behavioral impairments. The blood-brain barrier (BBB) regulates molecular exchange between the brain and the periphery, and its dysfunction could influence Aβ accumulation and neuronal damage. We hypothesize that a compromised BBB increases Aβ accumulation, exacerbating neurodegeneration. To test this, we will use the Drosophila melanogaster model, which is widely employed in neurodegenerative disease research due to its genetic tools and experimental accessibility. Transgenic fly strains expressing human $A\beta_{1-42}$ in glial cells were used. Similarly, BBB disruption was induced by RNAi-mediated knockdown of the moody receptor, essential for maintaining BBB integrity and permeability. Flies were aged and histological brain sections were analyzed for signs of neurodegeneration, such as vacuolization, and apoptosis, using TUNEL and anti-cleaved Dcp-1 staining. We also focused on the anatomy of the mushroom bodies, critical brain structures associated with memory and learning in flies. By comparing neuropathology in flies with normal versus disrupted BBB, we aim to determine how BBB integrity influences Aβ-induced damage. We expect that BBB dysfunction will increase neurodegeneration, supporting the notion that the BBB is essential in preventing misfolded protein accumulation and maintaining brain homeostasis. This project highlights the utility of *Drosophila* to study the BBB role in neurodegenerative diseases such as AD.

Reorganization of brain connectivity with age: dynamic simulations and topological analyses in human structural networks

Maria Rosalba Pineda Aguiar[1,2], Antonio Jiménez-Marin[3,4], Jesus Cortés[3,5,6], Patricio Orio[1,7]

(1) Centro Interdisciplinario de Neurociencia de Valparaíso, Valparaíso, Chile.
(2) Programa de Magíster en Ciencias Biológicas mención Neurociencias, Facultad de Ciencias, Universidad de Valparaiso, Valparaiso, Chile
(3) Computational Neuroimaging Lab, Biocruces-Bizkaia HRI, Barkaldo, Spain.
(4) Biomedical Research Doctorate Program, University of the Basque Country (UPV/EHU), Leioa, Spain.
(5) IKERBASQUE Basque Foundation for Science, Bilbao, Spain.
(6) Department of Cell Biology and Histology, University of the Basque Country (UPV/EHU), Leioa, Spain.
(7) Instituto de Neurociencia, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile.

Brain aging involves alterations in structural and functional connectivity, affecting the modular organization of neural networks. In this study, DTI and fMRI imaging data from 147 individuals aged between 10 and 80 years were analyzed to construct structural (SC) and functional connectivity (FC) matrices. Analysis with Graph theory tools reveals a decrease in topological segregation with age, reflected in lower modularity and clustering coefficient, along with an increase in the participation coefficient, suggesting a compensatory reorganization towards greater integration. Using a dynamic mean field model (DMF) coupled to the SC, we simulated functional connectivity (sFC) and dynamic functional connectivity (dFC) patterns, that were optimized per subject through the global coupling parameter (G). Simulated FC was compared with empirical data using Pearson correlation, while dFC was assessed via the Kolmogorov-Smirnov distance between empirical and simulated matrices. Significant correlations were found between topological metrics of structural connectivity (such as density and modularity) and the richness of simulated dynamics, suggesting that certain structural properties condition the brain's capacity to sustain multiple functional states. These findings provide insights into how aging-related changes in structural organization may lead to modifications in brain functional dynamics, offering a computational framework to study trajectories of healthy or pathological aging and potential functional biomarkers.

Funding: This work was supported by Grants Fondecyt 1241469 and Basal AFB240002 (ANID, Chile) to PO. MP is recipient of a FIBUV PhD fellowship (Universidad de Valparaíso).

Assessment of spatial concordance in visual field simulation using a novel training lens for Goldmann perimetry

Constanza Huete Gómez[1], Constanza Benavides Rivero[1], Fabiola Cerfogli Coppa[1], Iván Plaza Rosales[1,2], Nicole Herrera Toro[1], Hernán Torres Rivera[1]

(1) Universidad de Chile, Department of Medical Technology, Faculty of Medicine, Avenida Independencia 1027, Independencia, Santiago, Chile
(2) Universidad de Chile, Department of Neurosciences, Faculty of Medicine, Av. Independencia 1027, Independencia, Santiago, Chile

Background: Training in Goldmann perimetry faces challenges due to its subjective nature and the lack of validated simulation tools for visual field defects. To address this shortcoming, we have designed and evaluated a prototype lens that simulates visual impairments such as hemianopia, comparing the results regarding image characteristics and simulated defects.

Methods: We conducted a longitudinal observational concordance study involving 12 participants (10 students, two experts). Students simulated visual field defects using both goggles and the novel lens. Drawings made by experts were used as a control. Vectorized isopters from Goldmann fields were analyzed using Hausdorff distance, Fréchet distance, Structural Similarity Index (SSIM), Jaccard index,

and a compound similarity score integrating spatial and angular features.

Results: The lens prototype showed statistically significant improvements in similarity metrics compared to goggles. The isopter V4 had the most consistent improvement (Hausdorff $p = 0.00084$), with SSIM scores exceeding 0.80 in all student-lens trials. Jaccard index showed moderate variability but favored the lens condition. The compound similarity score reflected better structural alignment with expert tracings (mean values: V4=83.41%, I4=77.85%, I2=71.73%). Satisfaction surveys indicated positive user experience (α-Cronbach = 0.77), with the lens rated as more realistic, usable, and precise.

Conclusion: The new simulation lens provides a validated, reusable, and structurally accurate visual field defect training tool. Its integration into ophthalmologic education could improve student accuracy and standardize learning in kinetic perimetry.

Keywords: Visual field simulation; Goldmann perimetry; spatial concordance; medical education; Jaccard index.

Funding: Acknowledgments: We acknowledge the support of the Fondo Concursable de Investigación DETEM2024 - 570494

Brain Age Estimation Using Electroencephalography (EEG) Recordings and Machine Learning Techniques

Felipe Carriel[1], Agustin Ibáñez[2], Pavel Prado[3], Mónica Otero[1](1) Universidad San Sebastián, Facultad de Ingeniería, Santiago, Chile
(2) Universidad Adolfo Ibáñez, Instituto BrainLat, Santiago, Chile
(3) Universidad San Sebastián, Facultad de Ciencias de la Rehabilitación y Calidad de Vida, Santiago, Chile

Brain age estimation has emerged as a promising tool for assessing neurological aging and detecting brain deterioration before the onset of clinical symptoms. Unlike chronological age, the brain biological age can serve as a functional biomarker for identifying processes associated with neurodegenerative diseases. In this context, electroencephalography (EEG) stands out as an accessible and non-invasive technique for developing brain clocks. This study focused exclusively on the alpha band (8–13 Hz) due to its prominence in EEG recordings and its well known relationship with aging. A total of 1,287 EEG recordings from healthy participants in Latin America and Europe were analyzed. EEG neural generators were estimated using LORETA, calculating current density in 90 cortical regions defined by the AAL90 atlas. Spectral features were extracted from both the canonical and personalized alpha band, the latter based on each individuals peak frequency. These features were used to train various machine learning models (Lasso, ElasticNet, KNN, SVR, XGBoost, and multilayer neural networks) to estimate brain age. Performance was evaluated using MAE and R^2, with XGBoost standing out as the best model (MAE = 7.18, R^2 = 0.79). Nonetheless, all algorithms showed consistent results. The findings demonstrate that the alpha band contains sufficient information to build accurate models of brain aging, reinforcing its potential as an early biomarker in clinical settings for detecting neurodegenerative changes.

Funding: Fondecyt Iniciación 11241484, Basal FB21008, Exploración 13240042Vicerrectoría de Investigación y Doctorados, Universidad San Sebastián, Beca Doctorado FOLIO N° 80034658

Effect of chronic stress on information transmission between the mPFC and HPC during spatial learning

Yael Flores Pimentel[1,4], Lorena Chacana[4], Ignacio Negrón-Oyarzo[2,3], Nélida López Quilodrán[4], Javier Palma Espinosa[1], Patricio Orio[1,2]

(1) Centro interdisciplinario de neurociencia de Valparaíso, Pasaje Harrington 287 2340000 Valparaíso, Valparaiso ·, Chile
(2) Universidad de Valparaíso, Instituto de Neurociencia, Facultad de Ciencias, Gran bretaña 1111, Valparaíso, Chile
(3) universidad de valparaíso, Instituto de Fisiología, Facultad de Ciencias, Gran bretaña 1111, Valparaíso, Chile
(4) Universidad de Valparaíso, Facultad de ciencias, gran bretaña 1111, Valparaíso, Chile

Stress has been positioned as one of the main influences on neuronal circuit disorders. The synchronization between the medial prefrontal cortex (mPFC) and the hippocampus (HPC) has been observed to be affected by stress, suggesting functional implications.
In a Barnes maze spatial learning task, stressed animals show optimization in search strategies for escape, although the time required to complete the task is longer. In order to find a neurophysiological correlate to this behavior, we studied several measures of functional connectivity and information transfer between the LFP recorded in mPFC and HPC, recorded simultaneously during a learning trial. Our results reflect changes in sample entropy at the multiscale level, with significant changes in high gamma, i.e., between 50 and 100 Hz in the medial prefrontal cortex during training. Applying mutual information to the signals from both brain regions, according to the expert's expertise, reveals greater statistical dependence in the experimental group compared to the control group.

Funding: Fondecyt grant 1241469 and Basal grant AFB240002 (ANID, Chile)

Spatial Transcriptomic Mapping of Brain Gene Expression in Socially Isolated Female Mice

Camila Ramirez-Burgos[1], Adolfo Agurto[1], Karina Oyarce[2], Carlos Farkas[3], Antonia Recabal-Beyer[1]

(1) Universidad de Concepción, Departamento de Biología Celular, Facultad de Ciencias Biológicas, Concepción, Chile
(2) Universidad San Sebastián, Facultad de Medicina y Ciencia, Concepción, Chile
(3) Universidad Católica de la Santísima Concepción, Facultad de Medicina, Concepción, Chile

Social isolation is a chronic psychosocial stressor that affects both humans and social animals, leading to behavioral and physiological alterations. At the brain level, it primarily

impacts the limbic system, which includes regions such as the hippocampus, prefrontal cortex, amygdala, hypothalamus, and olfactory areas. Several of these structures exhibit sex-specific structural and transcriptional differences, resulting in differential stress responses. For instance, changes in brain volume in the hippocampus, amygdala, and hypothalamus, as well as alterations in the blood-brain barrier of the amygdala, have been observed exclusively in isolated females. However, most studies on the effects of social isolation on the brain have been conducted in males and have focused on specific brain regions, thus limiting a comprehensive understanding of the phenomenon.
This study proposes a broad and simultaneous transcriptomic analysis of multiple brain regions in adult female mice, both grouped and subjected to eight weeks of social isolation. Coronal brain sections between bregma -2.0 and -2.3 mm, embedded in paraffin, were analyzed using next-generation sequencing with 10x Genomics. The data were aligned with hematoxylin and eosin (H&E) stained micrographs as a reference. Through bioinformatic analysis of the transcriptomic profiles, anatomical identities were assigned to each region, and differentially expressed genes following social isolation were evaluated.
This study provides a comprehensive transcriptomic analysis that deepens the understanding of the female brain's response to social stress from a spatially integrative perspective, uncovering underlying molecular mechanisms with potential clinical relevance.

Funding: FONDECYT 11240516

Synergistic high-order statistics in a neural network is related to task complexity and attractor characteristics

Andrés Montenegro[1,2], Patricio Orio[1,2,3], Ignacio Ampuero[1], Javier Díaz[1]

(1) 1Centro Interdisciplinario de Neurociencia de Valparaíso, Valparaíso, Chile
(2) universidad de valparaíso, Instituto de Neurociencia, ciencias, Valparaíso, Valparaíso
(3) Advanced Center for Electrical and Electronic Engineering AC3E, Valparaíso, Valparaíso

Emergence of collective functions the brain is an open question in neuroscience, as they are believed to underlie consciousness, behavioral outputs, and brain disorders. It is unknown how measurable emergent behaviors can originate and be sustained, contributing to information processing. We studied the self-emergence of high-order interactions (HOIs) in RNNs that undergo plasticity to learn to perform cognitive tasks of different complexity. HOIs are statistical structures that are present in a group of variables but not in pair-wise interactions, and are characterized by tools from Information Theory. We trained continuous-time RNNs to perform one of the following tasks: Go/NoGo,Intensity Discrimination, Temporal Discrimination, Context-dependent Decision making. Then, the dynamics of the hidden layer was evaluated. HOIs were characterized using the O-info and S-info metrics, at different orders of interaction taking all combinations from 3 to 16 nodes. HOIs were evaluated using the O-info and S-info metrics across different interaction orders, considering all combinations from 3 to 16 nodes, and using three types of inputs: (i) the task the network was trained on, (ii) mixed-task inputs, and (iii) phase-randomized versions of the previous inputs. After training, the hidden-layer dynamics exhibit HOIs that are predominantly redundant for the training task and more synergistic for unseen tasks. Synergy increases with task complexity, whereas the simplest task (Go/NoGo) yields the greatest redundancy. Moreover, synergy is associated with more complex dynamics, as reflected by higher-dimensional trajectories.

Funding: This work is funded by Fondecyt grant 1241469 (ANID, Chile). AC3E is funded by Basal grant AFB240002 (ANID, Chile)

Information integration across brains: testing the IIT's exclusion postulate with hyperscanning EEG data

Diego Becerra Quispe[1], Ivo Leiva[4,5], Pedro Mediano[3], Ignacio Ampuero[1], Patricio Orio[1,2]

(1) Universidad de Valparaiso, Faculty of sciences, Gran Bretaña 1111, Valparaiso, Chile
(2) Universidad de Valparaiso, Centro Interdisciplinario de Neurociencia de Valparaiso, Valparaiso, Chile
(3) Imperial College London, Department of Computing, Exhibition Road, South Kensington, SW7 2AZ, London, United Kingdom
(4) Universidad de Chile, CIAE, Center for Advanced Research in Education, Santiago, Chile
(5) Pontificia Universidad Catolica de Chile, School of Psychology, Santiago, Chile

Unraveling the biophysical mechanisms underlying conscious experience is a challenging task. Integrated Information Theory (IIT) proposed measuring consciousness by calculating the integration of information in the activity of a system composed of several timeseries (e.g. voltage or fluorescence recordings). This framework was derived from phenomenological properties of conscious experience (Existence, Intrinsicality, Composition, Information, Integration, and Exclusion) spawning testable postulates. One particularly elusive postulate is exclusion, which states that systems composed of overlapping units (e.g. EEG channels, cells) cannot be conscious at the same time. Instead, it is the subsystem with the maximal value of information integration the one that is conscious, and calculating it requires finding the minimally informative bipartition (MIB) of that subsystem. Nevertheless, due to the computational cost of calculating integrated information for large systems, the predictions stemming from the exclusion postulate have not been tested with real data so far.

To test this postulate, we used an hyperscanning dataset, where 15 same-sex pairs of participants (7 male-male dyads, mean age = 27.9 years, SD = 7.1 years) performed a cooperative joint reaction time task; while their cortical activity was being recorded (32-channel EEG each, 1000 Hz sampling rate, online filtered 0.01—250 Hz). In order to calculate integrated information, we implemented a spectral clustering algorithm and several subsampling strategies. As a control, we simulated multivariate normally distributed timeseries from pairs of covariance matrices.

The MIB cuts across participants' brains as expected in the real data, but not in the simulated data. Thus confirming part of the IIT predictions.

Financing: Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) Patricio Orio grant number 1241469; ANID-Basal: Patricio Orio grant number AFB240002; Agencia Nacional de Investigación y Desarrollo (ANID) Doctoral Fellowship: Diego Becerra 21210914.

Cortico-cochlear Oscillatory Dynamics and Residual Inhibition in Chronic Tinnitus: Insights from EEG and DPOAE Analyses

Simón San Martín[1,5], Cristina De Gatica[1], Constantino Dragicevic[1], Vicente Medel[3], Christ Devia[1,4], Paul H. Delano[1,2,5]

(1) Universidad de Chile, Department of Neuroscience, Santiago, Chile
(2) Hospital Clínico Universidad de Chile, Department of Otorinolaringology, Santiago, Chile
(3) Universidadd Adolfo Ibáñez, Latin American Brain Health Institute (BrainLat), Santiago, Chile
(4) National Centre for Artificial Intelligence, CENIA, Santiago, Chile
(5) Advanced Center for Electrical and Electronic Engineering, AC3E, Federico Santa María Technical University, Valparaiso, Chile

Tinnitus, the perception of sound without external stimuli, involves both peripheral and central auditory pathways. This study investigates cortical and cochlear oscillatory activity during residual inhibition (RI), the temporary suppression of tinnitus following broadband noise exposure.
In this case-control study, 22 participants with unilateral chronic tinnitus and normal hearing thresholds were classified as responders (≥30% reduction in tinnitus perception post-noise, n=10) or non-responders (<30%, n=12). Simultaneous EEG and distortion product otoacoustic emissions (DPOAE) were recorded before and after 180 seconds of Gaussian noise exposure. Analysis included relative power in Delta, Theta, Alpha, Beta, and Gamma bands, and aperiodic components.
Results showed distinct neurophysiological patterns between groups. At Fz, non-responders exhibited lower pre-stimulus Delta power compared to post-stimulus ($p=0.013$), while responders showed increased post-stimulus Beta activity ($p=0.042$). Pre-stimulus 1/f slope differed significantly between groups ($p=0.006$). At the cochlear level, non-responders demonstrated increased Theta, Beta, and Gamma power, while responders showed reduced Alpha and Beta activity.

These findings suggest potential biomarkers for predicting tinnitus therapy responses and highlight the importance of cortico-cochlear interactions in RI. Future research should include larger samples, longitudinal data, and explore individual variability in auditory efferent function.

Funding: Financing: This research was supported by FONDECYT grant #1220607 for tinnitus mechanism investigation and AFB240002. Beca Doctorado Nacional ANID 2022-21221090 for SSM.

A Library of Electrophysiological Responses in Plants - Conduction Velocity across Species

Carla Contreras[2], Matias Morales[2], Patricio Rojas[2], Étienne Serbe-Kamp[1], Timothy Marzullo[1]

(1) Backyard Brains, Research and Investigation, Mesón de Paños, 6, Madrid, Spain
(2) Universidad de Santiago de Chile, Departamento de Biología, Chile

Electrical signaling is ubiquitous across life domains. We have previously demonstrated the presence of wound or tactile electrophysiological responses in a variety of both rapid movement (Sensitive Mimosa, Venus Fly Trap) and non-rapid movement plants (Tomato, Mint, Rosemary, etc.). Here, we measured the conduction velocity of impulse propagation in the same group of species plus others. We found that conduction velocities in rapid movement plants are 3 times faster (~30 mm/s) than non rapid-movement (~5-10 mm/s). We also note that plant conduction velocities are up to 10,000x slower than neuron conduction velocities (1-90 m/s). Whether plant impulse propagation is passive or active is an area of continued investigation.

Gap junction Innexin-2 modulates eclosion behavior in Drosophila melanogaster

Angelina Palacios Muñoz[1,3,4], Isaac García[1,3,4], Álvaro Monsalve[3], Javier Cavieres[3], Liliana Bustos[3], John Ewer[2,3]

(1) Universidad de Valparaiso, Facultad de Odontología, Subida Carvallo 211 Playa Ancha, Valparaiso, Chile
(2) Universidad de Valparaíso, Instituto de Neurociencia, Facultad de Ciencias, Avenida Gran Bretaña 1111, Playa Ancha, Valparaiso, Chile
(3) Centro Interdisciplinario de Neurociencia de Valparaíso, Universidad de Valparaíso, Valparaiso, Chile
(4) Centro de Investigación en Ciencias Odontológicas y Médicas (CICOM), Facultad de Odontología, Universidad de Valparaíso, Subida Carvallo 211, Playa Ancha, Valparaiso, Chile

Circadian clocks coordinate internal physiology with environmental day-night cycles through tissue-specific molecular oscillators. In Drosophila melanogaster, the central pacemaker in the brain synchronizes peripheral clocks to regulate rhythmic behaviors such as adult emergence (eclosion). While neuropeptidergic signaling from the brain to the peripheral clock in the prothoracic gland (PG), an endocrine organ controlling ecdysone release, is well established, the role of electrical synapses in this coupling remains unclear.
Here, we investigated the function of the gap junction protein Innexin-2 in eclosion rhythmicity. Knockdown of Innexin-2 in the PG resulted in a markedly arrhythmic eclosion pattern. Similarly, its knockdown in central clock neurons disrupted eclosion timing without affecting locomotor rhythmicity, indicating distinct mechanisms for these outputs. Functional assays in ex vivo PG preparations showed that Innexin-2–dependent coupling is sensitive to extracellular calcium and pH, as assessed by ethidium bromide dye transfer. Additionally, Innexin-2 knockdown in

the PG impaired the circadian regulation of ERK phosphorylation, a critical event in the PTTH-MAPK-ecdysone signaling pathway.
Our findings identify Innexin-2 as a key mediator of circadian output in the PG and demonstrate that electrical synapses contribute to central–peripheral clock coupling in Drosophila. This work highlights that environmental cues may fine-tune circadian outputs by modulating electrical coupling, expanding our understanding of the integration between chemical and electrical signaling in circadian regulation.

Funding: Centro de Investigación en Ciencias Odontológicas y Médicas (CICOM), Centro CIDI-5, Universidad de Valparaíso.

Electrophysiological Signatures of Consciousness During Sleep: Evidence from Lucid Dreams, Sleep Paralysis, Out-of-Body Experiences and False Awakenings

Nerea L. Herrero[1], Yohann Corfdir[1], Aylin A. Vázquez-Chenlo[1], Lucila Capurro[1], Cecilia Forcato[1]

(1) Laboratorio de Sueño y Memoria, Departamento de Ciencias de la Vida, Instituto Tecnológico de Buenos Aires (ITBA), Iguazú 341 (1437) Capital Federal, Buenos Aires, Argentina

Consciousness is typically absent during sleep, yet it can re-emerge in unique and immersive forms such as lucid dreams (LDs), sleep paralysis (SP), out-of-body experiences (OBEs), and false awakenings (FAs). Despite extensive phenomenological reports, the neurophysiological basis of these states remains largely unexplored.

We conducted overnight polysomnography in experienced individuals, capturing ten verified episodes (3 LDs, 2 SP, 2 OBEs, 3 FAs). Using a within-subject design, we compared each conscious episode to the same individual's standard sleep stages. Consciousness markers were identified through pre-agreed ocular signals. EEG spectral power was analyzed using principal component analysis (PCA) and permutation-based multivariate ANOVA (PERMANOVA).

These states differed markedly from wakefulness and did not fit a simple hybrid model between waking and sleep. Instead, they showed distinct neurophysiological signatures with partial overlap with REM and S1, but unique configurations in reduced-dimensionality space. Notably, we report the first in-lab identification of eye movement markers during OBEs and FAs, offering empirical validation for these experiences.
Spectral analysis showed LDs combined delta, theta, and low-gamma activity. SP episodes showed increased alpha, beta, low-gamma and reduced theta, consistent with heightened awareness. OBEs showed enhanced delta and theta, possibly reflecting sensory decoupling. One FA episode with lucidity markers resembled LDs in PCA space, suggesting shared neural features.

These findings challenge standard sleep classifications and support the existence of discrete, conscious brain states during sleep. By integrating subjective reports with EEG data, this study opens new avenues to investigate how consciousness transforms during sleep and how altered states like OBEs can be studied scientifically.

Targeting Cold Allodynia in Neuropathic Pain Using Novel Kv1.1 and Kv1.2 Channel Activators

Miguel Valencia Robles[1], María Pertusa[1], Rodolfo Madrid[1]
(1) Universidad de Santiago de Chile, Departamento de Biología, Facultad de Química y Biología, 9160000, Santiago, Chile

Painful hypersensitivity to innocuous cold, or cold allodynia, is among the most frequent and debilitating symptoms of neuropathic pain (NP) induced by peripheral nerve damage. Despite the advances in our understanding of the molecular and neural mechanisms underlying this sensory alteration, effective pharmacological treatments are still scarce. Several background, transduction, and voltage-gated ion channels functionally coexist to give shape to the net electrical response of peripheral nerve fibers involved in the responses to thermal stimulation. Among them, the Shaker-like Kv1.1 and Kv1.2 channels responsible for the brake potassium current I_{KD} play a critical role in the excitability of primary afferents under physiological and pathophysiological conditions, including NP. Despite its relevance in pain neurophysiology, chemical activators of Kv1.1 and Kv1.2 channels are very scarce, reducing the possibility of potentiating the activity of the functional channels that remain available under NP conditions. Nevertheless, it has been recently discovered that gallic acid and tannic acid, two organic compounds commonly found in several medicinal plants and astringent fruits, are strong activators of Kv1.1 and Kv1.2 channels. We wonder if the activation of brake channels using these compounds could reduce the thermal sensitivity of primary afferents and the allodynic phenotype in NP. Our preliminary results suggest that gallic acid shifts the thermal threshold of primary somatosensory neurons in culture to lower temperatures and reduces the cold-evoked allodynia in a model of NP in mice. These findings open an exciting opportunity to study these compounds as novel pharmacological modulators of Kv1 channels in NP.

Funding: Supported by VRIIC-DICYT 022443MM (RM, MP) and FONDECYT 1241513 (MP, RM).

NKCC1-mediated regulation of Long Term Potentiation in the Dentate Gyrus in the VPA model of autism

Carla Contreras Mena[1], Marcelo Lara[3], Elias Leiva Salcedo[2], Patricio Rojas[1]

(1) Laboratorio de Neurociencia, Universidad de Santiago de Chile, Facultad de Química y Biología, Santiago, Chile
(2) Laboratorio de Sistemas Neurales, Universidad de Santiago de Chile, Facultad de Química y Biología, Santiago, Chile
(3) Universidad San Sebastián, Facultad de Medicina y Ciencia, Concepción, Chile

Autism spectrum disorder (ASD) involves deficits in social behavior, spatial memory, and cognitive mapping—functions closely linked to the hippocampus. In ASD models, GABA remains excitatory in CA3 neurons postnatally due to elevated intracellular chloride, resulting from altered NKCC1 and KCC2 cotransporter activity. This chloride imbalance, also seen in temporal lobe epilepsy, may contribute to the

high prevalence of seizures in ASD. Using the valproate (VPA) model, we examined the role of NKCC1 in excitatory GABAergic signaling and its impact on synaptic plasticity in the dentate gyrus.
Extracellular field recordings were performed in acute hippocampal slices VPA-treated animals exhibited a more rapid induction and greater magnitude of long-term potentiation (LTP) compared to controls, suggesting increased excitability. Blocking NKCC1 with the diuretic bumetanide reduced this effect to levels similar to control, suggesting a change in the chloride driving force, turning GABA excitatory. It is excitatory synaptic plasticity. A decrease in Paired-Pulse Ratio (PPR) was observed after LTP induction in both groups, indicating a presynaptic component of LTP, which is unaffected by bumetanide. Properties of fIPSP in granule layer are not affected by inhibition of NKCC1 in both groups, this could mean that GABA interneurons from other layers are involved in alteration of fEPSP. These results suggest that NKCC1 is functionally active in the dentate gyrus and contributes to altered synaptic plasticity in the VPA model. This mechanism could represent a key driver of the synaptic impairments characteristic of ASD.

Funding: DICYT Regular - 022343RM - Participación del transportador de cloruro NKCC1 en la generación de crisis epilépticas en un modelo animal de autismo.

Cerebellar projections to the nigrostriatal pathway and its contribution to Parkinson's Disease

Maritza Oñate Valenzuela[1,2], Valentina Urra[1], Jorge Vera[2], Julian Guarque-Chabrera[2], Kamran Khodakhah[2]

(1) Universidad Mayor, Centro de Biología Integrativa, Facultad de Ciencias, Santiago, Chile
(2) Dominick P. Purpura, Department of Neuroscience, Albert Einstein College of Medicine, Bronx, New York, USA

Parkinson's disease (PD) is a neurodegenerative disease affecting the dopamine neurons in the substantia nigra compacta (SNc) which target the striatum (ST), comprising the nigrostriatal pathway (SNc-ST). The cerebellum is a major structure involved in motor and non-motor functions and evidence suggests also a role in PD, however the cerebellum has often been overlooked and studied as a separate component from the SNc-DST. Recently, we have described that the cerebellum sends direct glutamatergic projections to the SNc neurons, rapidly increasing SNc activity, providing a direct link between the two systems.
By using different tracing techniques, we delineated the sub-circuits conveying cerebellar signals to the SNc-ST. We identified cerebellar inputs in the three deep cerebellar nuclei (DCN) giving rise to SNc-disynaptic projections to the medial and lateral ST (DMS and DLS), as well as a topographical organization in the SNc neurons receiving DCN inputs and projecting to DMS and DLS, respectively. Furthermore, tracing of inputs to the three DCN labelled neurons at the SNc, suggesting for the first time a reciprocal pathway from SNc back to the cerebellum. Functional experiments by optogenetic activation of cerebellar inputs to the SNc produced an increase in striatal dopamine levels, as well as in the speed and probability of walking of mice.
We found a tight linear correlation between these two variables, suggesting a role for this pathway in movement vigor. Further experiments characterizing the changes associated in PD will provide the basis for targeting the circuit to test the therapeutic potential of this pathway.

Hippocampal Synchrony Dynamically Gates Cortical Connectivity Across Brain States

Guillermo Lazcano[1], Mauricio Caneo[1], Alejandro Aguilera[1], Germán Fernández[1], Ariel Lara-Vásquez[1], Nelson Espinosa[1], Pablo Fuentealba[1]

(1) Pontificia Universidad Católica de Chile, Psiquiatría, Medicina, Marcoleta 391, Santiago, Chile

Memory consolidation is thought to rely on hippocampo-cortical dialogue orchestrated by three cardinal sleep oscillations: cortical slow oscillations, thalamic spindles, and hippocampal sharp-wave ripples. However, how hippocampal outputs are routed to specific cortical targets and dynamically regulated across brain states remains incompletely understood. Here, we performed simultaneous multisite recordings from the dorsal and ventral hippocampus, and frontal and parietal cortex in rats alternating between wakefulness and sleep. Frontal slow oscillations operated as a global clock, resetting thalamic circuits and initiating spindle volleys that propagated from anterior to posterior cortex, while parietal slow oscillations more effectively recruited hippocampal ripples. Hippocampal ripples reflected anatomical connectivity, as dorsal ripples preferentially enhanced parietal spindles, whereas ventral ripples engaged mainly frontal spindling.
Notably, when ripples synchronized in dorsal and ventral hippocampus, local excitatory drive sharply decreased and neuronal spiking redistributed, associated cortical slow oscillations and spindle responses diminished, and cortical neuronal reactivation was suppressed, indicating that dorso-ventral ripple synchrony gates, rather than amplifies, hippocampo-cortical communication.
This gating effect was most evident through interactions with brain state, as dorsal-driven reactivation persisted across vigilance states, while ventral pathways were more pronounced during sleep. Collectively, our results outline a multilayer architecture in which slow oscillations provide a global temporal scaffold, spindles implement anatomically specific reactivation channels, and ripple coordination gates hippocampo-cortical communication, likely shaping the precision and specificity of memory consolidation within a highly variable neural substrate.

Funding: ANID | Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) : Pablo Fuentealba 1230589Agencia Nacional de Investigación y Desarrollo (ANID) : Pablo Fuentealba ACT210053Vicerrectoría de Investigación (VRI), Pontificia Universidad Católica de Chile

Cholinergic transmission modulates the excitability of lamp5 interneurons in layer 1a of the prefrontal cortex

Paula Leyton[1], Elias Leiva[1], Denise Riquelme[1]

(1) University of Santiago, Department of Biology, Faculty of Chemistry and Biology, 3363 Libertador Bernardo O'Higgins Avenue, Santiago, Chile

Acetylcholine (ACh) is a neuromodulator that regulates neuronal excitability. In layer 1 of the neocortex, neurogliaform interneurons are modulated by ACh in a receptor-type-dependent manner. In the somatosensory cortex, they are inhibited via M1 muscarinic receptors, while in the auditory cortex, NDNF interneurons are excited through nicotinic receptors. In this context, NDNF interneurons coexpress the LAMP5 marker, forming part of the neurogliaform interneuron population. NDNF interneurons control top-down information flow by modulating neuronal excitability through inhibition of the distal dendrites of pyramidal neurons from layers 2/3 and 5. However, until recently, it was unknown whether the LAMP5 interneuron population is also modulated by cholinergic stimuli. Recently, we identified that this type of interneuron is indeed modulated by cholinergic stimulation, as the activity of LAMP5 interneurons located in layer 1a of the prefrontal cortex is controlled by carbachol. Specifically, our results show increased excitability in LAMP5 interneurons of layer 1a, which may have implications for signal integration. The sensitivity of these interneurons to cholinergic stimuli could allow them to act as a dynamic filter that regulates access to top-down signals.

Funding: "Role of the UP and DOWN excitability states of VIP and SST interneurons in the dynamic frequency change between cortical layers of the medial prefrontal cortex". FONDECYT 1220680. 2022-2026.

High-Gamma Synchronization Between Lateral Entorhinal Cortex and Prefrontal Cortex Emerges with Executive Control in a Reversal Task

Alejandro Aguilera[1], Guillermo Lazcano[1], Mauricio Caneo[1], Nelson Espinosa[1], Pablo Fuentealba[1]

(1) Pontificia Universidad Católica de Chile, Department of Psychiatry, Faculty of Medicine, Marcoleta 391, Santiago, Chile

Executive function, the ability to adapt behavior to maximize goal achievement, relies on coordinated activity across distributed brain networks such as the prefrontal cortex (PFC) and the hippocampus (HIP). The lateral entorhinal cortex (LEC), a hub for temporal and contextual information, has dense reciprocal connections with the PFC and HIP, yet its contribution to executive function remains largely unexplored.
LEC–PFC circuit interactions were investigated during a spatial reversal learning task by simultaneously recording local field potentials from LEC, PFC, and hippocampal CA1 in rats across 10 behavioral sessions. Behavioral performance improved significantly over days, accompanied by a shift toward more effective strategies.
Spectral analyses revealed no changes in local power spectral densities in any region across training, indicating stable within-region dynamics. In contrast, phase coherence analyses identified a significant increase in high-gamma (70–100 Hz) synchronization between LEC and PFC from day 1 to day 10. The magnitude of this increase correlated with performance gains, suggesting that enhanced inter-regional coupling accompanies behavioral adaptation. Spatial mapping further revealed that the observed gamma coherence increase was concentrated in the maze's central arm, immediately before the choice point, suggesting a role in decision-making processes.

These findings demonstrate that improvements in executive function are associated with strengthened high-frequency coordination between LEC and PFC, without changes in local oscillatory content. This pattern suggests that the engagement of executive control recruits a more synchronized LEC–PFC network, potentially facilitating the rapid exchange of task-relevant information at critical moments for behavioral choice.

Funding: Fondecyt Regular 1230589

Partitioning Neural and Vascular contributions to fMRI-BOLD variability in aging

Daniel Franco OByrne[1], Ana Castro-Laguardia[1], Josefina Cruzat[1], Carlos Coronel-Oliveros[2], Vicente Soto[5], Cecilia Gonzalez-Campo[4], James Shine[3], Agustin Ibañez[1,2], Enzo Tagliazucchi[1], Vicente Medel[1]

(1) Universidad Adolfo Ibañez, Latin American Brain health Institue, Diagonal las torres, Peñalolen, Santiago, Chile
(2) Trinity College, Dublin, Ireland
(3) Unersity of Sydney, Sydney, Australia
(4) Universidad San Andres, Buenos Aires, Argentina
(5) Universidad Adolfo Ibañez, Centro de neurociencia social y cognitiva, Psicologia, Santiago, Chile

Introduction
Aging induces complex alterations in brain function, structure, and metabolism, yet the specific neural and vascular contributions to these changes remain unclear. BOLD fMRI signal variability is a promising biomarker reflecting both neuronal and hemodynamic dynamics, but its interpretation in aging is complicated by neurovascular changes, particularly in the hemodynamic response function (HRF). This study investigates neural and vascular contributions to BOLD variability changes using the LEMON database (N=200; EEG and fMRI).

Methods
Structural MRI assessed gray matter atrophy (FreeSurfer) and white matter hyperintensities (WMHs) using the Lesion Segmentation Toolbox. Resting-state fMRI quantified BOLD variability as the standard deviation of the signal; HRF was estimated and deconvolved using the rsHRF toolbox to separate neural and vascular influences. EEG data were source-reconstructed with MNE-Python, with 1/f slope and spectral parametrization computed to characterize circuit-level aging. General Linear Models analyzed relationships among structural, neurovascular, and electrophysiological measures at the parcel level (Desikan-Killiany atlas).

Results
Age correlated significantly with BOLD variability before HRF deconvolution ($p < 0.001$), but this association disappeared

after deconvolution (p = 0.1), indicating vascular factors drive BOLD variability changes. HRF peak height correlated with WMH burden and EEG 1/f slope but not with deconvolved BOLD variability. Moreover, parcel-wise age effects on HRF aligned with gray matter atrophy patterns, highlighting neurovascular-structural aging interactions.

Conclusion

Age-related BOLD variability changes primarily reflect vascular rather than neural alterations. The findings highlight the need for computational models incorporating spatially and individually varying HRF to improve understanding of brain aging dynamics.

Funding: FONDECYT de Inicio 11251578

Chemogenetic Rescue of PV Interneuron Dysfunction After Adolescent Ketamine Exposure

Sashá van Buuren Briones[1,2,3], Felipe Guiffa[1,3], Freddy Aguilar[1,3], Angélica Escobar[1,4], Marco Fuenzalida[1,4]

(1) Centro de Neurobiología y Fisiopatología Integrativa (CENFI), Instituto de Fisiología, Facultad de Ciencias de la Universidad de Valparaíso, Av. Gran Bretaña Nº 1111, Playa Ancha, Valparaiso, Chile
(2) Programa de Magister en Ciencias, Mención Neurociencias, Facultad de Ciencias de la Universidad de Valparaiso, Av. Gran Bretaña Nº 1111, Playa Ancha, Valparaiso, Chile
(3) Programa de Doctorado en Ciencias, Mención Neurociencia, Facultad de Ciencias de la Universidad de Valparaiso, Av. Gran Bretaña Nº 1111, Playa Ancha, Valparaiso, Chile
(4) Millennium Nucleus of Neuroepigenetics and Plasticity (EpiNeuro), Santiago, Chile

Ketamine is a rapidly acting antidepressant that has gained increasing use in clinical practice. However, recreational use of subanaesthetic doses carries significant neurodevelopmental risks. Adolescence is a critical period for brain maturation, and ketamine exposure during this stage has been associated with long-lasting deficits in object discrimination and recognition memory in adulthood. These impairments have been linked to reduced inhibitory function in the Dentate Gyrus (DG), a hippocampal subregion crucial for pattern separation. Notably, parvalbumin-expressing interneurons (PV-INs)—a major fast-spiking inhibitory population in the DG—appear to be particularly vulnerable to adolescent ketamine exposure.

Subanaesthetic ketamine administration during adolescence has been shown to disrupt the fast-spiking properties of PV-INs in the adult brain, reducing their excitability and weakening local inhibitory control. This disruption leads to a shift in the excitatory/inhibitory balance within the DG. Based on this, we hypothesized that restoring PV-IN fast-spiking activity would ameliorate ketamine-induced deficits in pattern separation. To test this, we employed PV-Cre transgenic mice to selectively express the excitatory DREADD hM3Dq in PV-INs. Chemogenetic activation of these neurons restored their fast-spiking properties and enhanced excitability, thereby rescuing dysfunctional DG circuitry. The present findings suggest that targeted modulation of PV-INs may represent a therapeutic strategy to counteract the long-term cognitive effects of adolescent ketamine exposure.

Financing: FONDECYT 1121173 to Marco Fuenzalida, FONDECYT 11240331 to Angelica Escobar, CIDI N°1 (CENFI-UV) to Marco Fuenzalida, and ANID MILENIO NCN2023_32, to Marco Fuenzalida.

Evaluation of the effect of superoxide dismutase 2 (SOD2) overexpression in dopaminergic neurons during aging in Drosophila melanogaster

Amalia Chamorro González[1], Paula Amado Hinojosa[1], Jorge M Campusano[1]

(1) Pontificia Universidad Católica, Ciencias Biológicas, Facultad de Ciencias Biológicas, Av. Libertador Bernardo O'Higgins 340, Santiago, Chile

Aging is a process driven by the accumulation of cellular damage, leading to a gradual deterioration of body functions. One of the phenotypes associated with aging is the loss of motor ability, which could be explained by an increased vulnerability of dopaminergic neurons to oxidative stress.
A key indicator of aging is the deterioration of mitochondrial function. Superoxide dismutase 2 (SOD2) is an enzyme that neutralizes superoxide generated as a byproduct of cellular respiration. Its deficiency causes an increase in oxidative stress, contributing to cellular damage and neuronal dysfunction, which could underlie the neurodegeneration of dopaminergic neurons in aged animals.
Results from our laboratory indicate that in a Drosophila melanogaster wild-type strain, the exponential phase of mortality begins 50 days after hatching. Locomotion and climbing ability decrease significantly at 30 and 40 days of age, respectively. Furthermore, global degeneration of dopaminergic neurons is recorded at 60 days of age.
Here, SOD2 was overexpressed exclusively in Drosophila dopaminergic neurons. Interestingly, this manipulation delayed deaths in females flies, different from males of the same genotype and their genetic controls. We are evaluating whether these animals exhibit alterations in locomotor ability, and at least 10 days post-eclosion, no significant differences in climbing ability were observed compared to controls. Furthermore, we are quantifying the number of dopaminergic neurons and dopamine levels throughout aging in these animals. We hope to test the hypothesis that SOD2 overexpression provides protection against age-associated dopaminergic neurodegeneration and locomotor decline.

Funding: Fondecyt 1231556 (Dr. Jorge Campusano) and ANID Doctoral Scholarship 21221779 (Paula Amado Hinojosa)

Sustained analgesic effects of psilocybin in a rat fibromyalgia model

Estibaliz M. Ampuero Llanos[1], Luis Constandil[1], Fernando Ortiz-Cisternas[1], Alejandro Hernandez[1], Carlos Gil[2], Leopoldo Naranjo[2], Antonella Osses-Toledo[1], Jeffri S. Retamal[1]

(1) Universidad de Santiago de Chile, Departamento de Biología, Facultad de Química y Biología, Santiago, Chile (2) SPORA BIOTECH, Santa Clara 684, Santiago, Chile

Chronic pain is a leading cause of disability worldwide, reducing productivity and increasing the risk of opioid overdose. Recently, uncontrolled and biased studies have suggested that psilocybin-enriched extracts may alleviate symptoms of depression, anxiety, phantom limb pain, and migraine. However, these findings remain inconclusive and underscore the need for rigorous, controlled studies. Here, we tested the analgesic potential of psilocybin in a fibromyalgia-like model induced by neonatal limited beading (NLB) in rats, which induces generalized hyperalgesia in adulthood. Hyperalgesia was assessed by the Randall–Sellito test, revealing a decrease in the paw withdrawal thresholds. Meanwhile, a single acute intraperitoneal dose of psilocybin (2 mg/kg) rapidly reduced hyperalgesia, while a 10-day low-dose regimen (0.3 mg/kg, intraperitoneal) induced sustained analgesic effects lasting up to 40 days. To evaluate the spinal nociceptive processing, we recorded C-reflex responses evoked by tibial and sural nerve electrical stimulation, and further examined diffuse noxious inhibitory control (DNIC) using a contralateral conditioned paw pressure stimulus. An intrathecal dose of psilocybin extract (0.03 and 0.3mg/kg) reduce the nociceptive signal. Furthermore, we evaluate the rat's behavior after the psilocybin-treated measuring anxiety (elevated plus maze), working memory (Y-maze) and locomotor activity (open field maze). The results showed that psylocibin reduce anxiety without changing locomotor activity. Together, these results showed that psilocybin produces both acute and long-lasting antinociceptive effects in a preclinical model of fibromyalgia and support its usage as a novel therapeutic approach for chronic widespread pain.

Funding: Vinculab 25-6, Science-up USACH



Sociedad Chilena de Neurociencia

XXI REUNIÓN ANUAL

Campus de Isla Teja
Universidad Austral, Valdivia
1 al 3 de octubre de 2025.