**Poster Session 2: Thursday, 4th November, from 09:00 to 12:30, Exhibition Hall.**

PS2-01

# ADAMTS2 and Poly (I:C): Genetic and enviromental mouse models of Schizophrenia disorder.

Miss Celia Martín-Cuevas[1,2], Mr Víctor Darío Ramos-Herrero[2], Dr. Susana García-Cerro[1,2], Dr. Manuel Canal-Rivero[1,2,3], Miss Nathalia Garrido-Torres[1,2,3], Mr. Idalino Rocha-González[1,2,3], Dr. Miguel Ruíz-Veguilla[1,2,3,4], Dr. Benedicto Crespo-Facorro[1,2,3,4], Dr. Ana Carmen Sánchez-Hidalgo[1,2]

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Schizophrenia (SCZ) is a neurodevelopmental psychiatric disorder that affects 1% of the world's population. Theories suggest that SCZ is caused by genetic and environmental factors, with strong epidemiological evidence showing an association between maternal infection during pregnancy and development of SCZ in offspring in adult life. In recent years, our group has described a set of six overexpressed genes associated with the appearance of the disease (ADAMTS2, CD177, CNTNAP3, ENTPD2, RFX2 and UNC45B). ADAMTS2 was the most overexpressed gene in independent samples of patients and was moderated by the antipsychotic action in responsive patients. We propose two animal models to reproduce the cerebral and behavioral symptoms of SCZ disorder. We have generated a transgenic mouse model that selectively overexpresses ADAMTS2 in brain regions under CaMKIIα promoter. We have also established a maternal immune activation (MIA) mouse model with Polyinosinic-polycytidilic acid (Poly (I:C)), a synthetic analog of double-stranded RNA that triggers a citokine-associated immune response. Pregnant dams are exposed to viral agent during gestation. In the last described model, we found weight differences and an altered body temperature in injected pregnant females with Poly (I:C). Positive, negative and cognitive symptoms are evaluated in Poly (I:C) model through behavioral tests. Results show defects in social and sensorimotor gating tasks without affected locomotion. All experiments are performed both in female and male mice, since SCZ affects patients of both sexes differently. On the other hand, different brain parameters have also been evaluated, such as cortical thickness and its layers (I-VI) and dendritic spines density. Our results suggest differences in cortical thickness and decreased dendritic spines density in adult offspring. Finally, both models separately and its combination will permit us evaluate genetic and environmental theories and will help us advance in the knowledge and treatment of SCZ disorder.

PS2-02

# CHROMATIN SIGNATURES OF NEURONAL SUBPOPULATIONS WITH DIVERGENT PROJECTION AT THE MIDLINE IDENTIFY NOVEL WIRING REGULATORS

Dr. Marta Fernández-Nogales[1], María Teresa López-Cascales[1], Dr. Rafael Muñoz-Viana[1], Dr. Jordi Fernández-Albert[1], Dr. Verónica Murcia-Belmonte[1], Dr. Ángel Barco[1], Dr. Eloísa Herrera[1]
[1]*Instituto de Neurociencias, Alicante, Spain*

Therapeutic approaches aimed to restore the function of damaged neuronal circuits will benefit from a better understanding of the mechanisms driving and constraining circuit assembly. The binary decision of crossing or avoiding the midline that retinal ganglion cells (RGCs) axons take at the optic chiasm during embryonic development is essential for binocular vision and represents a simple and robust model to identify novel mechanisms controlling axon guidance decisions during circuits formation. By comparing the transcriptome and chromatin occupancy profiles of crossed and uncrossed RGCs, we identified key differences between these two populations of neurons. Our unbiased screens revealed important differences in the expression of guidance molecules and the binding of transcription factors to regulatory regions, exposing novel transcriptional mechanisms underlying axon guidance decisions. Functional in vivo experiments with candidate genes validate this approach and reveal the implication of several transcription factors, such as the Lhx family, in the navigation of RGC axons. Overall, our study retrieved novel factors controlling axon guidance, thereby contributing to a better understanding of the transcriptional regulatory logic underlying neuronal connectivity.

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PS2-03

# A ribo-tag based screen identifies a cohort of proteins locally translated at the axons during axonal navigation

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Local translation in the growth cone has been proposed as a mechanism for rapidly producing proteins "on demand" during axonal navigation in the developing embryo. The binary decision of crossing or not the midline that visual axons take at the optic chiasm attending to attractive or repulsive signals, is an ideal model to investigate the molecular mechanisms underlying axon pathfinding. By using a cre-dependent Ribo-Tag mouse line (translated ribosome affinity purification) crossed with two cre-lines specific for retinal neurons that cross or not the midline, we have isolated mRNAs locally translated in contralateral or ipsilateral axons respectively. By high resolution FRAP (fluorescence recovery after photobleaching) visualization of Venus-3UTR constructs in axons navigating the optic chiasm, we confirmed axonal translation of the mRNAs identified in our screen. Interestingly, the axonal translatome obtained from these two populations of retinal neurons includes a subset of genes enriched in common elements of cytoplasmic polyadenylation that are known to activate specific mRNAs for local protein translation. These findings confirm for the first time the existence of local protein synthesis in the cone of growing axons in vivo. In addition, they reveal the translatome of contralateral and ipsilateral axons and provide a deeper understanding of the molecular machinery involved in axon guidance decisions.

PS2-04

# Developmental-based classification of neurons in the chicken central extended amygdala

Ms. Alessandra Pross[1,2], Mr. Alek Hanafi Metwalli[1,2], Dr. Ester Desfilis[1,2], Prof. Loreta Medina[1,2]
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The amygdala is extremely complex and heterogeneous, and contains different neuron subpopulations involved in functions essential for survival. It plays a key role in the stress response in mammals, but very little is known on its role in non-mammals. In order to improve welfare in laying hens, it is crucial to disentangle amygdalar structure and function in these animals. In mammals, two major populations of peptidergic neurons of the central extended amygdala (EAce), containing somatostatin or enkephalin, become active (on) or inactive (off) during stress response. These cell types originate in different embryonic domains and express different region-specific transcription factors during development. The evolutionary developmental biology approach has provided crucial information on how the amygdala develops in different vertebrates, which has become essential to identify homologous cell populations across species. Our goal was to identify neurons of the chicken EAce homologous to those of mammals using this approach. In particular, we investigated the embryonic origin of enkephalin and somatostatin neurons of the EAce in domestic chicks (Gallus gallus domesticus), by studying their co-expression with different region-specific developmental transcription factors. We performed double labelling experiments combining chromogenic or fluorescent in situ hybridization for enkephalin and somatostatin with immunohistochemistry or immunofluorescence for the transcription factors Pax6, Nkx2.1 and Islet1. We found that: (1) enkephalinergic cells of the capsular and peri-interpeduncular parts of the EAce express mainly Pax6, which is specific of cells derived from the dorsal striatal embryonic division; and (2) the somatostatinergic cells express mainly Nkx2.1, typical of cells derived from the pallidal embryonic division. These results support the hypothesis of homology of these neurons between mouse and chicken, and set the basis to study their function during the stress response. The results also contribute to extract general developmental-based principles on the neural architecture of the central extended amygdala of amniotes.

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PS2-05

# Wnt1 effect on the Fasciculus retroflexus axonal navigation.

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During development of the neuronal system, immature neurons must generate their dendritic arborizations and axonal neurites properly. The developing axons follow a stereotypic map between short and long range signals. The haptotaxis mechanism involves short range signals that require cell-cell contact and they produce permissive or avoidance territories for the growing axons. Meanwhile, the quimiotaxis process is related to long range signals that are able to attract or repeal the growth of the axons towards the sources. One clear example are the fasciculus retroflexus axons, that, as they reach the diencephalic floor plate vicinity, bend caudalwards. Then, they navigate crossing the midbrain until their target in the rostral hindbrain. They must cross the Isthmic territory, a well-known secondary organizer, that contains several morphogens such as Fibroblast growth factor 8 (Fgf8) and Wingless (Wnt1). Our aim in this work is to unveil the Wnt1 role in the determination of the mid-hindbrain territory crossed by the fasciculus retroflexus and how it affects the guidance mechanism needed by this tract. We used a Wnt1 lack of function transgenic mice and analyzed its phenotype by immunohistochemistry, axonal tracing dyes and iDisco techniques. The results obtained showed that the mesencephalic basal territory was severely affected. The axons were able to travel caudally but displayed strong abnormalities in their direction. The isthmic territory in the absence of Wnt1 was not able to properly induce the surrounded territories triggering a dramatic alteration of the correct pathway cues needed for the fasciculus retroflexus axons.
Work supported by MINECO/AEI/FEDER (SAF2017-83702-R), GVA (PROMETEO/2018/041), ISCIII (“RD16/001/0010”), co-funded by ERDF/ESF, “Investing in your future”, and FTPGB (FTPGB18/SM) to S. Martinez; MECD (FPU16/03853) to V. Company. The Institute of Neurosciences is a “Centre of Excellence Severo Ochoa (SEV-2017-0723)".

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PS2-06

# Wnt1 role in the specification and differentiation of the habenular complex.

Ms. Ana Moreno Cerdá[1], Ms Verónica Company[1], Ms Raquel Murcia-Ramón[1], Dr. Abraham Andreu-Cervera[1], Ms Francisca Almagro-García[1], Dr Salvador Martínez[1], Dr Diego Echevarría[1], Dr Eduardo Puelles[1]
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The neuroblasts of the developing neural tube requires the activity of precise regions (secondary organizers; SO) to direct their specification and differentiation programs. Along the antero-posterior axis, it has been described three SO: the isthmic organizer, the zona limitans and he anterior neural ridge. They produce secreted signaling molecules named morphogens. These mainly include Fibroblast growth factor 8 (FGF8), Bone morphogenetic proteins (BMP), Wingless (WNT1) and Sonic Hedgehog (SHH). In fact, some of them organize more precisely the dorso-ventral patterning of the neural tube. Thus, SHH is produced mainly in the floor/basal plate and BMP with WNT1 on the roof plate.

Based on our interest in the limbic system development, we studied the WNT1 role in the specification and differentiation of the habenular complex. This neuronal structure is located at the dorsal aspect of the thalamic prosomere, central part of the diencephalic territory. We analyzed in a Wnt1 loss of function murine model the embryonic development of this neuronal complex. This study has included different approaches that has included proliferation, immunohistochemistry and iDisco techniques. The lack of function of this morphogen produced a severe alteration in the proliferation rates and a dramatic extension in the anteroposterior dimension of the habenular complex. The subnuclei subdivision in the components of the lateral and medial habenula maintained a similar distribution. Therefore, Wnt1 is necessary for the correct habenular complex growth but not for their specification and differentiation.

Work supported by MINECO/AEI/FEDER (SAF2017-83702-R), GVA (PROMETEO/2018/041), ISCIII ("RD16/001/0010"), co-funded by ERDF/ESF, "Investing in your future", and FTPGB (FTPGB18/SM) to S. Martinez; MECD (FPU16/03853) to V. Company. The Institute of Neurosciences is a "Centre of Excellence Severo Ochoa (SEV-2017-0723)".

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PS2-07

# Otp expression in cortical neurons throughout ontogenesis

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Different studies have shown the important role of embryonic origin to understand the mature phenotype of neurons. Recently, we described a new radial telencephalon-opto-hypothalamic embryonic domain, coexpressing the transcription factors Foxg1 and Otp, which produces the vast majority of the glutamatergic cells of the medial extended amygdala, as well as some cells of the pallial amygdala. To determine if there are other pallial populations that co-express both transcription factors, we used Otp-eGFP transgenic mice and double immunofluorescence for Foxg1 and GFP at different embryonic stages and postnatal ages. From middle embryonic stages, we observed very few GFP/Otp expressing cells, with migratory neuroblast morphology, in the primordium of the anterior cingulate cortex, mostly intermingled with fibers of the developing cingulate fascicle. These cells were in continuity with similar cells and fibers found in the septo-preoptic region, resembling a ventro-dorsal tangential migratory stream. The number of cells and fibers in this stream increased during development. Postnatally, some scattered cells were observed in the mantle of the neocortex, mostly in the cingulate cortex and adjacent cortical areas. All of them coexpressed Foxg1. Moreover, other GFP/Otp cells were found in the hippocampal complex. A densely packed group was found in the pre/parasubicullum, which gave rise to a projection to the hippocampal formation. The latter also included some cells, which coexpressed Foxg1. The finding of GFP/Otp cells in the neocortex and hippocampal complex raises questions on their origin, phenotype and function throughout ontogenesis. The location of some GFP/Otp cells in relation to developing septal and cingulate fiber bundles suggest a role as guidepost during fascicle development. Otp may also be important for the migration and differentiation of specific cortical neurons. In addition, as Otp is also expressed in adulthood, it may be playing a regulatory role affecting mature cortical function.

*E.D and L.M contributed equally as supervisors of this work.

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PS2-08

# Expression of gonadal hormones' receptors in Otp-related social behavior network

Ms. Alba Gonzalez-Alonso[1,2], Ms Lorena Morales[1,2], Doctor Antonio Abellán[1,2], Professor Loreta Medina[1,2], Doctor Ester Desfilis[1,2]

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The brain of vertebrates includes a social behavior network, responsible for producing and regulating social interactions in a flexible and dynamic way. Social behaviors, like mating, parental care and aggression, show strong variations between sexes and are regulated by gonadal hormones. Many of the areas of this network express estrogen and androgen receptors. These brain areas include multiple neuron populations with specific connections, but the relation between gonadal receptors and specific neuron populations is poorly understood. In this study, we took advantage of the Otp-eGFP transgenic mice, with permanent labelling of Otp cells and their axonal projections, to study the relation between gonadal hormones' receptors and Otp cells. Otp is a transcription factor critical for the differentiation of neuroendocrine neurons in the hypothalamus and also for the generation of glutamatergic neurons of the medial extended amygdala. We studied the expression of estrogen receptors alpha (Erα) and beta (Erβ) and the androgen receptor (AR), in areas rich in Otp neurons and in Otp neurons' targets. To study receptor expression, we used in situ hybridization method. Otp cells and fibers were visualized using immunohistochemistry to detect GFP. The study was performed in two developmental stages, before and after sexual maturation. The results show that in both stages there is a high expression of receptors in areas rich in Otp cells, like the medial amygdala, especially its posterodorsal subdivision, the BSTM and the paraventricular hypothalamic nucleus. We also observed a high expression of receptors in targets rich in Otp-expressing terminals, such as the lateral septum, the medial preoptic region, the ventromedial hypothalamic nucleus and the periaqueductal gray. The fact that the Otp-related social behavior network expresses gonadal receptors suggests a prominent role of these cells and their connections in regulating sexual and other social behaviors.

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PS2-09

# Astrocytes gate spike timing dependent plasticity in the Nucleus Accumbens

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The nucleus accumbens (NAc) is a pivotal locus for reward-related behaviours and addiction circuitry. It is mainly composed by medium spiny neurons that receive dopaminergic and glutamatergic afferents. The glutamate homeostasis in the NAc is regulated by the glutamate transporter 1 (GLT-1), a highly specific glutamate electrogenic transporter that is expressed on astrocytes. GLT-1 controls signal transmission uptaking glutamate from the synaptic cleft and thus controlling the time course of excitatory postsynaptic currents and potentials. Drugs of abuse causes glutamatergic dysregulation in the NAc and a downregulation of GLT-1 after prolonged drug-withdrawal. Although numerous studies show that GLT-1 regulate the synaptic plasticity triggered by different cell conditioning paradigms like spike timing-dependent plasticity (STDP). In STDP, the temporal coincidence of pre- and postsynaptic spiking activity leads to long-term potentiation or depression. However, the role of astrocytes in the regulation of NAc plasticity induced by drugs of abuse is poorly understood.

In this study, we combined cell biology and electrophysiological approaches in brain slices, to test the hypothesis that dopaminergic activity alters the expression of astrocytic GLT1 and regulates the time course of glutamatergic synaptic transmission in the NAc. Astrocytic activation with opto-stimulation of dopaminergic axons, or with different drug abuse or with selective stimulation via DREADDs decreases GLT-1 functionality and glutamate synaptic currents in astrocytes. Furthermore, we found an increase in time and space of glutamate in the synaptic cleft modifying the kinetic of excitatory postsynaptic potentials. This phenomenon allowed us to find a temporal window between presynaptic activity and postsynaptic spikes in STDP paradigm in which the synaptic weigh was modified after drugs of abuse, adjusting the computational ability of the system during addiction.

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PS2-10

# Neuromuscular activity regulates PKA catalytic and regulatory subunits and its downstream signaling pathway for ACh release at the NMJ

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Protein kinase A (PKA) triggers intracellular pathways that modulate activity-dependent mechanisms such as neurotransmission and synaptic plasticity. At the neuromuscular junction (NMJ), PKA signaling enhances neurotransmitter release via the phosphorylation of the release machinery including SNAP-25 (synaptosomal associated protein of 25 kDa) which is a key protein for the exocytosis. Presynaptic impulse at the NMJ triggers the molecular mechanisms associated with the release of ACh and this process can be retrogradely regulated by the resulting muscle contraction. Therefore, both presynaptic and muscular regulation could influence PKA signaling pathway, although this regulation is unknown.
Accordingly, to study the effect of synaptic activity on PKA subunits and its activity, we stimulated the rat phrenic nerve (1 Hz, 30 min) resulting or not in contraction (abolished by μ-conotoxin GIIIB). Changes in protein levels and phosphorylation were detected by Western blotting and cytosol/membrane translocation by subcellular fractionation.
We show that muscle contraction decreases PKA-Cβ levels because the contraction-induced upregulation of AKAP150 is capable to recruit enough RIIβ regulatory subunits to permit Cβ catalytic subunits increase their activity enhancing pSNAP-25 T138 phosphorylation and synaptic vesicle exocytosis and, therefore, allowing the myocyte to receive enough ACh to complete a correct contraction. In addition, RIIα opposes to this regulation binding to Cβ to inhibit its activity and stops the ACh liberation mechanism contributing to balance the catalytical activity of Cβ on pSNAP-25 T138. This contraction-induced regulation opposes to the performed by the presynaptic stimulus that balancing the same mechanisms maintain stable endogenous pSNAP-25 T138 levels and therefore ACh exocytosis.
These results indicate that neuromuscular synaptic activity performed by the neuron and the myocyte regulates accurately the PKA catalytic and regulatory subunits in order to maintain an optimal ACh transmission at the NMJ.

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PS2-11

# Basal autophagy inhibition in microglia diminishes phagocytosis of apoptotic cells and microglial survival

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Autophagy is the cellular process whereby cytoplasmic constituents such as long-lived proteins and damaged organelles are delivered to the lysosome for degradation. Autophagy is basally active in virtually all cell types, wherein it functions as a cellular quality control checkpoint to promote cellular fitness and survival. However, the role of basal autophagy in microglia, the brain resident macrophages, has started to emerge only recently. In this study, we have evaluated the effect of basal autophagy inhibition in microglial phagocytic function and survival. To monitor the autophagic activity of microglia, we first developed a 2-step model to separately assess autophagosome formation and degradation in microglia using conventional LC3 Western blot assays. Using this model, we confirmed that after treatment with the unc-like kinase1/2 (ULK1/2) inhibitor MRT68921, which inhibits the autophagy pre-initiation complex, reduced both autophagosome formation and degradation proportionally in primary microglia, leading to a reduced turnover ratio of autophagosomes and an inhibition of basal autophagy. Next, we assessed the effects of basal autophagy inhibition in microglial phagocytosis of apoptotic cells and survival using pharmacological in vitro and genetic in vivo approaches. In vitro, MRT68921 impaired microglial phagocytosis of apoptotic cells at low concentrations that did not induce microglial death. However, high concentrations of MRT68921 did induce significant microglial death, suggesting that basal autophagy disruption is critical for microglial survival. In vivo, constitutive deletion of autophagy-related genes such as ATG4B, also disrupted microglial phagocytosis and decreased microglial survival in the neurogenic niche of the hippocampus, where newborn neurons constantly undergo apoptosis and are rapidly engulfed by microglia. We are now extending our analysis to other microglia-specific autophagy-deficient mouse models such as ULK1 or BECN1. In conclusion, our results indicate that basal autophagy shapes microglial fitness regulating their function and survival.

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PS2-12

# Modification of the extracellular matrix impairs microglial motility

Dr. Federico Soria[1,2,3], Lic. Irene Tomé-Velasco[1]

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Beyond neurons and glia, the Central Nervous System (CNS) holds a plastic scaffold known as the extracellular matrix (ECM). Unlike the ECM from connective tissue, where collagen is the main unit, the neural interstitial matrix consists mostly on long chains of the glycan polymer hyaluronan. Protein components of the ECM bind to hyaluronan forming a self-assembled matrix that functions as structural framework and signalling hub. Microglia, the never-resting immune cell of the CNS, constantly surveys the brain parenchyma, interacting with neighbouring cells and the surrounding extracellular microenvironment. We have recently described in adult parkinsonian mice a bidirectional loop between hyaluronan and microglia, which affects both matrix structure and microglia reactive state, with consequences on neurodegeneration and tissue architecture (Soria et al., 2020, Nat Commun). Despite recent advances on matrix-glia interplay, it is unknown whether changes in the structural matrix affect microglial motility. Here we report on the interaction between microglia and hyaluronan, using an ex vivo approach to characterise microglia dynamics in response to matrix modification. Using 2-photon time-lapse imaging in acute slices of Cx3cr1+/eGFP mice, we show that microglial motility, ramification and territory surveyed are reduced upon hyaluronan fragmentation ex vivo, with no changes when other matrix components are degraded instead. We also report alterations in directed motility upon laser ablation after hyaluronidase treatment. These results suggest impairment of microglial motility upon matrix modification and shed light on the dual role of hyaluronan as scaffolding polymer and pro-inflammatory signal in the CNS.

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PS2-13

# Brain estrogen synthesis regulates synaptic inhibition in female hippocampus

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The aim of our work was to study the contribution of estrogen, the main feminine sex hormone, to the function of hippocampal inhibitory neurons (IN). IN play a critical role in controlling different forms of network activity and plasticity underlying cognition. Estrogens are synthesized in the brain by neurons that express the enzyme aromatase and regulate excitatory synaptic function and plasticity. However, the role of brain-derived estrogen role in controlling IN function is unknown.

We first studied the contribution of hippocampal CA1 IN to brain estrogen synthesis. We detected aromatase mRNA and protein in CA1 IN expressing the marker parvalbumin (PV), suggesting estrogen synthesis in this major IN subtype. We then studied the functional impact of brain estrogen synthesis on CA1 synaptic inhibition using patch-clamp recordings on brain slices from female ovariectomized mice. Our results revealed that blockade of brain aromatase increases CA1 synaptic inhibition by limiting the activation estrogen receptors and lead to maturation of perineuronal nets (PNNs), extracellular structures that control PV+ IN excitability. Enzymatic digestion of PNNs impaired aromatase regulation of synaptic inhibition, suggesting that plasticity of PNNs is part of the mechanism used by estrogen to regulate the function of PV+ IN.

Interestingly, aromatase regulation of PV+ IN was only present in female mice. Using a transgenic line in which sex determination is independent of sex chromosomes and manipulations of perinatal gonadal hormone levels, we found that female-specific regulation of PV+ IN has a gonadal origin and is independent of the genetic sex of the brain.

Our results reveal sex differences in the regulation of PV+ IN by brain synthesized estrogen. Since aromatase inhibitors are widely used in clinics, our results have implications for understanding the adverse effects that these treatments have on cognitive functions in humans.

PS2-14

# EFFECTS OF TRANSCRANIAL DIRECT-CURRENT STIMULATION (tDCS) ON THALAMOCORTICAL SENSORY PATHWAY IN AWAKE MICE

Mr. Guillermo Sánchez-Garrido Campos[1], Ms. Marta Estévez-Rodríguez[1], PhD Isabel Cordones[1], PhD Javier Márquez-Ruiz[1]
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The transcranial Direct-Current Stimulation (tDCS) is a non-invasive neuromodulatory technique that induces changes in the human cortex excitability dependent on the applied polarity. It has recently been proposed that tDCS may act by modifying the local- and long-range circuits involved in the excitation/inhibition (E/I) balance in the cerebral cortex. The aim of the present study was: 1) to describe the characteristics of field potentials recorded in primary somatosensory cortex (S1) in response to whisker and ventro-posterior medial thalamus (VPM) electrical stimulation, and 2) to compare the effects of tDCS on field potentials induced by these two different stimuli.

For that, we prepare C57 mice for chronic multilayer recording of LFPs, VPM electrical stimulation and tDCS in the alert head-restrained condition. tDCS was applied between a ring electrode over S1 and a reference electrode consisting of a rubber rectangle (6 cm2) attached to the back of the mouse. Evoked potentials in response to whisker or VPM stimulation were chronically recorded at two different depths (400 - 600 µm and 1000 – 1500 µm from the brain surface) before, during and after short pulses of tDCS (15 s) at different transcranial current intensities (±50, ±100, ±150 and ±200 µA).

The recorded VPM-induced potentials showed a reduction in the latency (~3 ms) of the first component with respect to whisker-induced sensory potentials. On the other hand, depth profile of VPM-induced evoked potentials showed the inversion of N1 component across layers similarly to reported for whisker-induced sensory potentials. Regarding to immediate effects of tDCS, anodal and cathodal pulses of tDCS successfully modulated the waveform of VPM-induced evoked potentials increasing and decreasing its amplitude during anodal and cathodal, respectively.

These results demonstrate that tDCS immediate effects on S1 recorded VPM-induced potentials reproduce those observed in sensory evoked potentials induced in response to peripheral whisker stimulation.

PS2-15

# Characterization of synaptic transmission occurring in olfactory glomeruli of X. tropicalis tadpoles in vivo

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Communication among neurons occurs in synapses in a highly regulated process that determines the way we see, smell or behave. In the olfactory system, the glomeruli of the olfactory bulb are the first site of odour processing in the brain. Here, many synapses are established between olfactory sensory neurons and olfactory bulb neurons. The western-clawed frog (Xenopus tropicalis) provides an excellent experimental platform to investigate the molecular mechanisms of synaptic transmission in vivo due to its experimental accessibility, transparency and possibilities of genetic manipulation. The aim of the present study is to characterize the bases of neurotransmission taking place in olfactory glomeruli. We investigated long-lasting depolarizations (LLDs) that were identified in local field potential recordings obtained from the glomerular layer of the olfactory bulb. Odorant responses were obtained after ipsilateral stimulation of the olfactory epithelium with amino acid solutions. Amino acids applied at 200 µM triggered responses in the majority of animals investigated: arginine 82% (n=9), histidine 76% (n=9), leucine 77% (n=14) and methionine 63% (n=39). This evidence shows a poor selectivity of the olfactory system of X. tropicalis tadpoles to detect odorants. To assess sensitivity, methionine was applied from 0.01 µM to 200 µM. The threshold for detecting responses was found at ~1 ?M. The experimental approach was refined using the zHB9::GFP transgenic line, which allowed the recording of a single identified glomerulus. The amplitude of LLDs obtained after 20 µM and 200 µM application of methionine changed from 27 µV (n=5) to 49 µV (n=5), respectively. This result suggests that the amplitude of LLDs obtained in olfactory glomeruli is related to the concentration of the odorant applied. Future experiments are required to determine the precise contribution of presynaptic terminals of olfactory sensory neurons to LLDs.

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PS2-16

# Towards pharmacological modulation of microglial phagocytosis

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Microglia, the immune cells of the central nervous system, display a variety of functions to maintain homeostasis in the brain. Microglia are professional phagocytes and remove apoptotic cells to prevent the spillover of toxic components. Although phagocytosis is a key process to maintain brain homeostasis and is very efficient in physiological conditions, little is known on how to modulate microglial phagocytosis when it is impaired or exacerbated, such as in epilepsy or schizophrenia, respectively. Therefore, our goal is to find pharmacological modulators of microglial phagocytosis. Using a high throughput screening strategy in primary cultures of microglia, we tested 600 compounds from the Prestwick library, already approved by the Federal Drug Administration (FDA) and the European Medicines Agency (EMA) to be used in humans, in an in vitro model of phagocytosis. We found a subset of drugs that could be classified as promoters of phagocytosis (pro-phagocytosis drugs) or inhibitors (anti-phagocytosis). To validate the phagocytosis modulators in a more complex system, we used organotypic cultures and confirmed that some compounds promoted phagocytosis, while others blocked it. Currently, we are validating the compounds in vivo in two different models: anti-phagocytosis drugs are tested against physiological phagocytosis of apoptotic newborn cells in the adult hippocampal neurogenic niche; pro-phagocytosis drugs are tested against the pathological phagocytosis impairment induced in a model of epilepsy by intrahippocampal administration of kainic acid. Considering the lack of strategies to modulate phagocytosis, our compounds may represent a new therapeutical strategy to restore brain parenchyma homeostasis in pathologies where phagocytosis is impaired or exacerbated.

PS2-17

# TRESK background potassium channel modulates thermal sensitivity in mice

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TRESK is a background potassium channel activated by intracellular calcium through the phosphatase calcineurin. The channel is highly expressed in distinct populations of primary sensory neurons involved in nociception, where it modulates their excitability. We previously described that TRESK ablation induces an increase in mechanical and cold sensitivity, and its downregulation after nerve injury has been linked to chronic pain. Interestingly, calcineurin inhibition by the drug tacrolimus (FK-506) can induce cold allodynia and hyperalgesia in human patients as a side effect. Here, we explore the behavioral effects of tacrolimus and the role of TRESK in the modulation of heat and cold sensitivity. First, we proved that the expression of major background potassium and TRP channels expressed in primary sensory neurons is not modified by TRESK ablation in the TRESK knockout mice model used in our studies. We also found that, in addition to its high expression in sensory ganglia, TRESK is also expressed at lower levels in spinal cord, brain, cerebellum and hippocampus. Behavioral studies show that, when exposed to a cold ramp, TRESK knockout mice present nocifensive behaviors in response to higher temperatures than wild-type animals. Interestingly, only wild-type male mice treated with tacrolimus present an enhanced sensitivity to cold. To better understand the cellular basis of this differences, responses to cold stimuli of different populations of primary sensory neurons are under study. TRESK ablation also induces an increase in heat sensitivity in male mice, but not in females. Besides, heat sensitivity of female mice is increased after tacrolimus treatment in a TRESK-independent manner. In summary, TRESK modulates cold sensitivity and its indirect inhibition by tacrolimus in wild-type mice resembles the cold allodynia observed in knockout animals. Given the channel's role in thermal sensitivity modulation and its mainly peripheral expression, TRESK activation is a potential therapeutic approach for the treatment of tacrolimus-induced allodynia and hypersensitivity to painful stimuli.

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PS2-18

# Pre- and postsynaptic organization of C-type synapses on motor neurons are regulated by the different isoforms of Neuregulin 1

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C-type synapses on motor neurons (MNs) originate from local cholinergic interneurons and display a particular postsynaptic ER-related organelle called subsynaptic cystern (SSC). Neuregulin-1 (NRG1) was detected close to C-boutons in association with SSCs. As the NRG1 antibody used in these studies cannot distinguish different isoforms of NRG1, we took advantage of transgenic mouse lines to examine NRG1 isoform-specific functions in C-boutons.

We have performed electron and confocal microscope analyses of the MN C-boutons of transgenic mice that overexpress NRG1 type I (NRG1-typeI) or NRG1 type III (NRG1-typeIII).

Samples from NRG1-typeIII mice showed NRG1 area that, in contrast with the wt mice, overpass the afferent presynaptic limits on the surface of MN cell bodies. We found that these C-boutons were specially enriched in sigma-receptor 1, Kv2.1 and M2 muscarinic receptor, with a similar pattern to the expanded NRG1-typeIII. However, the number of cholinergic terminals contacting MN somata was not altered. The examination of NRG1-typeIII mice by electron microscopy showed an accumulation of abnormally expanded and reduplicated SSC-like structure. Regarding NRG1-typeI, the immunostaining for NRG1 also produced a stronger signal at the MN surface of NRG1-typeI mice compared with WT. However, in contrast to NRG1-type III mice, the vesicular acetylcholine transporter immunostaining revealed an increase in the number and size of presynaptic terminals innervating the MN surface. The ultrastructural examination confirmed the presence of enlarged presynaptic terminals on the MN soma surface, matching partially with postsynaptic SSC. However, the amplified formation of SSC-like was not observed in NRG1-typeI mice.

Altogether, these findings suggest that: 1) NRG1-typeIII acts as a specific organizer of postsynaptic SSC-like membrane compartments without a major impact on the C-bouton presynaptic counterpart; 2) NRG1-typeI promotes presynaptic C-bouton synaptogenesis with no influence on biogenesis or molecular architecture of coaligned SSC.

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PS2-19

# Transcranial direct current stimulation effects across motor cortex layers on awake mice

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Transcranial direct-current stimulation (tDCS) is a non-invasive brain stimulation technique which involves the application of weak electric currents on the scalp. Although previous studies have demonstrated the value of tDCS for modulating sensory, motor, and cognitive functions, there are still lacks in our understanding of the underlying physiological mechanisms. To evaluate the impact of tDCS on cortical excitability, human experiments usually assess motor evoked potentials by motor cortex stimulation, for this reason, we aimed to stablish a mouse model of M1-tDCS in order to be able to explore physiological mechanisms of tDCS in more detail.

For this purpose, we performed electrophysiological recordings in M1 of alert mice during and after administration of M1-tDCS. Mice were prepared for chronic recordings of neuronal activity in layer 2-3, layer 5 and layer 6, evoked by stimulation of ventral lateral nucleus of the thalamus (VAL). M1-tDCS was performed at different current intensities (50, 100, 200 and 300 µA) for 5 s to test the acute effects on neuronal excitability, and for 15 min to analyze neuroplastic effects of the intervention.

tDCS acutely increased and decreased the amplitude of the VAL-evoked local field potentials (LFP) in a polarity- and intensity-dependent manner. We observed an increase of excitability for anodal stimulation, and a decrease for cathodal stimulation. This modulatory effect was observed across distinct cortical layers, but was more prominent for superficial layers. For 15 minutes of anodal or cathodal tDCS, we observed a similar polarity- and intensity-dependent modulation of the VAL-evoked LFP amplitude during stimulation, but when tDCS was switched off, only the protocols with higher intensities were able to induce a robust plastic effect, showing an increase of LFP amplitudes after anodal and a decrease after cathodal tDCS.

The current study demonstrates the feasibility of a mouse model of M1-tDCS that resembles the modulatory effects of the intervention observed in human experiments, highlighting the importance of properly adjusting the tDCS parameters to obtain results translationable to humans.

PS2-20

# The role of caspase 8 in the dopaminergic system

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Our group was a pioneer in identifying new non-apoptotic roles of caspases-8 and -3/7 in the CNS demonstrating a caspase-dependent mechanism governing microglia activation. Our propose is not only to continue studies about non-apoptotic roles of caspases in the control of brain inflammation, but to extend them to neuronal phenotypes. The aim of the present study was to understand the role of caspase-8 in the dopaminergic system. For this reason we have generated a novel animal model with a specific gene deletion of caspase-8 within catecholaminergic cells.

We performed behavioral, molecular and cellular analysis to study the nigro-striatal system in these animals. Therefore, we have measured dopamine levels in striatum by HPLC, expression levels of main dopaminergic components in substantia nigra by RT-PCR and motor status by behavioral tests. Our results show differences in the behavioral tests performed in mice lacking caspase-8. Moreover, we found no differences on mRNA expression levels of main dopaminergic proteins but higher levels of dopamine accompanied by an increase in the number of dopaminergic neurons by means of stereological studies. All these results could be the cause of the changes observed in the behavioral tests. Therefore, our results suggest that this animal model could open the field to future studies on the role of caspase-8 on the dopaminergic system, being applicable as a model for different brain disease with the dopaminergic system involved.

PS2-21

# ROLE OF PI3K CATALYTIC ISOFORMS IN NEURONAL METABOLISM

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Among all organs, the brain is unique, not only because it consumes 20% of total body glucose, but also due to its unique metabolic profile, which appears compartmentalized between astrocytes and neurons. Thus, under basal conditions, astrocytes are responsible for most glucose uptake, and its processing into lactate, which is then shared with neurons through the astrocyte-neuron lactate shuttle (ANLS). However, there is increasing evidence that these metabolic fluxes are modulated in response to neuronal activity.

Phosphatidyl inositol 3-kinases (PI3Ks) are lipid kinases responsible for the conversion of phosphatidylinositol (4.5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-triphosphate (PIP3). PI3Ks are important mediators of synaptic plasticity processes. In addition, the PI3K/mTOR pathway is a central hub for the regulation of energy balance and cellular metabolism. However, little is known about the function of PI3Ks in neuronal metabolism.

We have addressed this problem using two lines of loxP mice, for the main catalytic subunits of PI3K: p110α or p110β. Neuronal specific knock-outs (KO) are generated in the hippocampus of adult animals by injecting an adeno-associated virus that expresses the Cre recombinase under the neuron-specific αCamKII promoter. Mice injected with saline were used as control.

Using proteomic approaches, we have observed differential effects of p110α and p110β KO in glycolytic enzymes, as well as in proteins related to mitochondrial function. Alterations in mitochondrial function are also suggested by changes in mitochondrial morphology, as evaluated by electron microscopy.

The functional relevance of these changes and the implication of each PI3K catalytic subunit in neuronal metabolism and synaptic plasticity will be discussed.

PS2-22

# ROLE OF PI3-KINASE REGULATORY SUBUNIT (P85) IN THE STRUCTURAL PLASTICITY OF DENDRITIC SPINES

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Class I Phosphatidylinositol-3-kinases (PI3Ks) constitute a complex family of enzymes formed by a P110 catalytic (p110α, p110β, p110γ, p110δ) and a P85 regulatory (p85α, p55α, p50α, p55γ, p85β) subunit, with important roles in virtually all physiological processes in the body including, synaptic plasticity and cognitive function. Synaptic plasticity has a functional component (changes in synaptic strength) and a structural component (changes in synapse size, associated to cytoskeleton modifications in dendritic spines). The differential interactions and contributions of the PI3K isoforms for these functional and structural aspects of synaptic plasticity are still unknown. To address these issues, we have carried out loss-of-function (RNA interference) of specific p85 isoforms in rat hippocampal slices. After specific knockdown of p85α or p85β, most PI3K complexes are detected as heterodimers of p110 interacting with the alternative p85 isoform. In this manner, we can assess the function of p110/p85α versus p110/p85β forms of PI3K. This manipulation is associated with changes in PI3K signalling, as reported by phosphorylation of the protein kinase Akt and the ribosomal protein S6. In addition, using life imaging experiments in organotypic hippocampal slices, we detected changes in structural plasticity after long-term potentiation (LTP) induction, particularly with respect to the recruitment of the cytoskeleton proteins actin and cofilin into the dendritic spines. These differences had also functional consequences at the level of synaptic potentiation, as evaluated using electrophysiological recordings. The molecular aspects of this differential contribution of p85α and p85β to synaptic plasticity will also be discussed.

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PS2-23

# The microglial P2Y6 receptor mediates neuronal loss and memory deficits in neurodegeneration

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Summary

Microglia are implicated in neurodegeneration, potentially by microglia phagocytosing neurons, but it is unclear how to block the detrimental effects of microglia while preserving their beneficial roles. The microglial P2Y6 receptor (P2Y6R) – activated by extracellular uridine-5'-diphosphate (UDP) released by stressed neurons – is required for microglial phagocytosis of neurons. We show here that injection of amyloid beta (Aβ) into mouse brain induces microglial phagocytosis of neurons, followed by neuronal and memory loss, and this is all prevented by knockout of P2Y6R. In a chronic tau model of neurodegeneration (P301S tau mice), P2Y6R knockout prevented tau-induced neuronal and memory loss. In vitro, P2Y6R knockout blocked microglial phagocytosis of live but not dead targets, and reduced tau-, Aβ- and UDP-induced neuronal loss in glial-neuronal cultures. Thus, the P2Y6 receptor appears to mediate Aβ- and tau-induced neuronal and memory loss via microglial phagocytosis of neurons, suggesting that blocking this receptor may be beneficial in neurodegenerative diseases.

Keywords: Microglia, phagocytosis, neurodegeneration, P2Y6 receptor, memory deficits, Alzheimer's disease, cell death.

PS2-24

# RAS SIGNALING DURING METABOTROPIC GLUTAMATE RECEPTOR DEPENDENT LONG TERM DEPRESSION (mGluR-LTD).

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RASopathies are the most common type of neurodevelopmental disorders, affecting approximately 1 in 1000 individuals. Ras proteins are small GTPases that can act as a molecular switch with its downstream effectors, such as PI3K/Akt or MAPK/Erk pathways. Both, Ras and its effectors are essential regulators of cell proliferation, differentiation and survival. In addition, they have been related with synaptic plasticity events, key processes for learning and memory. It is known that Ras, PI3K/Akt and MAPK/Erk pathways are required for long term potentiation; however, the role of Ras in long-term depression induced by metabotropic glutamate receptors (mGluR-LTD) is still controversial but clinically relevant, especially for Costello Syndrome or SynGAP-deficient patients.

To address this question we generated a collection of Ras mutants and produced Sindbis virus to infect rat hippocampal organotypic cultures used for electrophysiological recordings and biochemical experiments. To monitor protein synthesis, we used SUnSET assay, a non-radioactive method based on the use of puromycin. We also optimized a FRET system in our organotypic cultures to monitor Ras activity using live imaging techniques. Firstly, using this FRET system, we observed that Ras activity increases upon chemical mGluR-LTD induction (DHPG 100µM stimulation) in dendritic spines. Subsequently, to elucidate if Ras is required for mGluR-LTD we occluded Ras activity using a dominant negative form which prevented the synaptic depression, measured electrophysiologically. Blocking Ras activity with this mutant also prevented the increase in pErk levels and in protein synthesis upon chemical mGluR-LTD induction compared to control infected slices. To sum up, Ras activity is required for mGluR-LTD, mediating the increase in Erk signaling and in protein synthesis.

PS2-25

# On the G protein-coupled heteroreceptor complexes neuromodulation of the Claustrum

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G protein-coupled receptors (GPCRs) modulate the synaptic glutamate and GABA transmission of the claustrum. The work focused on the transmitter-receptor relationships in the claustral catecholamine system and receptor-receptor interactions between, dopamine D2 receptor (D2R), kserotonin 5HT2A receptor (5HT2AR), neurotensin NTS1 receptor (NTS1R), kappa opioid receptors (KOR) and SomatostatinR2 (SSTR2) in claustrum. Methods used involved immunohistochemistry and in situ proximity ligation assay (PLA) using confocal microscopy. Double immunolabeling studies on dopamine (DA) D1 receptor (D1R) and tyrosine hydroxylase (TH) immunoreactivities (IR) demonstrated that D1R IR existed in almost all claustral and dorsal endopiriform nucleus (DEn) nerve cell bodies, known as glutamate projection neurons, and D4R IR in large numbers of nerve cell bodies of the claustrum and DEn. However, only a low to moderate density of TH IR nerve terminals was observed in the DEn versus de few scattered TH IR terminals found in the claustrum. These results indicated that DA D1R and D4R transmission in the rat operated via long distance DA volume transmission in the rat claustrum and DEn to modulate claustral-sensory cortical glutamate transmission. Large numbers of these glutamate projection neurons also expressed, 5-HT2AR, NTS1R, KOR and SSTR2 which formed 5HT2AR-D2R, D2R-NTS1R, and KOR-SSTR2 heteroreceptor complexes using PLA. Such receptor-receptor interactions can finetune the activity of the glutamate claustral-sensory cortex projections from inhibition to enhancement of their sensory cortex signaling. This can give the sensory cortical regions significant help in deciding on the salience to be given to various incoming sensory stimuli.

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PS2-26

# A comparative study of the somatosensory cortex and the hippocampus in adult mice. From the synaptome to the connectome.

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Unveiling the brain's map of connections has become one of our times' great current scientific challenges. For this purpose, we have developed a tracer tool within the software package Espina. In the present study, we have traced the skeletons of all the axons and dendrites. We have connected each skeleton with the 3D reconstruction of the synapses related to them.

Three male C57 mice were sacrificed at postnatal week 8. The brain was then extracted from the skull and processed for electron microscopy. Three-dimensional brain (neuropil) tissue sample from layers 1 (L1) and 3 (L3) of the somatosensory cortex (hindlimb representation) and another one from stratum radiatum (SR) of hippocampal CA1 were obtained using focused ion beam milling and scanning electron microscopy (FIB/SEM). Synaptic junctions were visualized, identified (excitatory/inhibitory), and segmented in 3D with Espina software. The axons and dendrites involved in establishing the synapses were then followed and traced through the stack of images.

In spiny dendrites, the linear density of synapses was higher in the SR (more than 3 synapses/µm) than in L1 and L3 (less than 2 synapses/µm). Most synapses were established on dendritic spines, although around 4% of spines did not establish synapses. In dendrites that lack spines, the mean density of synapses was also higher in the SR than in L1 and L3. The excitatory axons established more synapses per micron in the hippocampus (0.63 synapses/µm) than axons from the somatosensory cortex (0.46 and 0.41 synapses/µm in L1 and L3, respectively). However, the inhibitory axons had a similar linear density of synapses in all the regions studied (between 0.38 and 0.43 synapses/µm).

Each region manifests structural parameters that make them different from other regions. Dendrites and excitatory axons from the hippocampus have a higher density of spines and synapses than those from the somatosensory cortex. However, the inhibitory axons showed similar synaptic densities in all the samples. The tracer tool developed allows in-depth characterization of the connectome from brain samples.

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PS2-27

# NMDAr BLOCKING BY MK801 PRODUCES SPECIFIC OSCILLATORY CHANGES IN THE HIPPOCAMPUS AND THE PREFRONTAL CORTEX IMPAIRING WORKING MEMORY AND PLACE CELL FIRING

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Information processing in the brain depends on the dialog between different regions orchestrated by oscillatory activity, especially theta (4-12 Hz) and gamma rhythms (30-100Hz). Clinical and basic research has confirmed a strong relationship between cognitive impairment and distortion of these rhythms in Schizophrenia. It is hypothesized that these oscillopathies originate from alterations of the excitatory-inhibitory (E-I) balance. Therefore, unveiling the relationship between brain rhythms and cognition is crucial for understanding the cognitive manifestations of Schizophrenia. In this work, we aimed to investigate how changes in the E-I balance might reproduce rhythm and behavioral alterations. We used a mouse pharmacological model of schizophrenia, administering MK801 to adult wild-type mice, an NMDAr blocker known to alter interneuron and pyramidal activity. Mice were implanted with microdrives mounting tetrodes aimed to the dorsal hippocampus and medial prefrontal cortex (mPFC). Then brain activity was recorded while mice performed spontaneous exploration in an open field, and while testing working memory in the y-maze, after the administration of MK801 or vehicle. Our results proved that NMDAr blocking exerts differential effects in the oscillatory activity of the hippocampus and the mPFC. While in CA1 and subiculum MK801 produced an increase in gamma oscillations and a distortion of theta/gamma coupling, mPFC activity was characterized by an augmentation of theta, gamma and emergence of high frequency oscillations (HFO, 155-185 Hz). Interestingly HFO in the mPFC was strongly modulated by local theta activity. In addition, we observed an increase in CA1-mPFC coherence in the delta and alpha band, changes in locomotor behavior, defective place cell function and impaired working memory in the y-maze. We observed that CA1 theta/gamma modulation was enhanced during right alternation in the y-maze, but none of the oscillatory changes produced by MK801 could predict performance in the y-maze.

PS2-28

# Age-dependent neural coding in the basal forebrain during a Pavlovian task

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Acetylcholine mediates multitude of cognitive functions including arousal, attention, sensory processing, reinforcement expectation, reward and addiction. The basal forebrain cholinergic input to the cortical mantle plays a central role in these modulatory processes. Age-related changes in the morphology of cholinergic neurons has been observed across species, characterized by dendritic, synaptic, and axonal degeneration. However, the link between cholinergic activity during learning and the normal or pathological age-related neurodegeneration is still missing.

To clarify the role of the basal forebrain neurons in learning during the normal aging process, we performed neuronal recordings in the nucleus of the horizontal limb of the diagonal band, in head-fixed ChAT-cre mice during an auditory cued-outcome task. Animals from 3 to 18+ months of age were injected with an adeno-associated virus carrying channelrhodopsin-2, transfecting cholinergic neurons, allowing us to optically tag them.

Animals showed decreased anticipatory licking correlated with aging, being old animals less likely to lick during reward-predicting trials, compared to young ones. Surprisingly, tagged cholinergic neurons in the young animals seemed to respond to the reward but not punish-related cue, whereas in the old animals no response to tone was observed. Additionally, both punishment and reward activated part of the recorded neurons in all the animal groups, while only from 12+ months these contingencies had an inhibitory effect on the cell population.

We additionally performed fiber photometry experiments with a fluorescent sensor in order to determine the cholinergic influx over basolateral amygdala. Results showed a similar pattern to that observed in the basal forebrain cholinergic neurons.

These changes in coding of outcome contingencies of basal forebrain neurons can reflect the ongoing degenerative process or even be the cause, at least partially, of the learning deficits observed during natural aging.

PS2-29

# Dopaminergic blockades decrease physical exercise maintenance response.

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The motor responses during physical activity are the result of a hierarchically arranged central nervous system circuits. Motor programs planned in the prefrontal cortex, are refined in different cortical and subcortical circuits. Finally, the motor output arrives to the spinal cord, the first layer in the hierarchy of muscle control. One key aspect of the circuits involved in motor control is that they are modulable. In previous studies we determined that the physical capacity, measured as the maximal response during an incremental test, is dependent of D1 striatal and D2 extra-striatal actions in Sprague-Dawley rats. Here we want to determine the role of dopaminergic antagonists in physical activity maintenance responses.

For that aim, we first defined a model of physical activity maintenance that consisted in performing three incremental tests after a habituation protocol to forced wheel exercise, each one separated with three days with an active rest session to maintain the performance throughout the tests. In the second test, we administered a D1-like receptors antagonist (SCH23390) in a dose of 0.1 mg/kg intraperitoneally or saline (Sodium Chloride 0.9%).

Sprague Dawley rats administered with D1 SCH23390 (0,1mg/kg) antagonist decreased the performance in the second test compared to the first and third ones (Test 1: 25.39±4.58 min.; Test 2: 5 min. (SCH23390, $p<0.05$) and 23.06±6.42 min. (Saline); Test 3: 25.42±3.4 min.). Rats injected with saline were able to maintain the performance throughout the incremental tests. Rats injected with SCH23390 significantly decreased their performance in the second test but recovered performance in the third test. This suggests that a habituation protocol and active rests between tests allow the maintenance of the performance and that the dopaminergic system is involved in the maintenance response. Finally, our model significantly reduces the number of experimental animals.

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PS2-30

# Increased excitability of parvalbumin-positive interneurons in premotor cortical area in a mouse model of obsessive-compulsive disorder

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Obsessive Compulsive Disorder (OCD) is a severe, chronic, and ubiquitous neuropsychiatric disorder that affects 2-3% of worldwide population. A cortico-striatal dysfunction is considered a major factor in OCD pathogenesis. However, integration of other brain structures is necessary to generate a satisfying explanatory model of OCD pathophysiology and symptom generation. It has been reported in Sapap3 knockout (KO) mouse, a well-validated model of compulsive-like behavior, that striatal region receives increased levels of synaptic inputs coming from the secondary motor area (M2). M2 is thought to be homologous to the Supplementary Motor Area in humans, an area showing hyperactivity in OCD patients. SAPAP3 is a scaffolding protein of the glutamatergic synapses, predominantly expressed in the striatum and cortical areas, whose absence has been associated with obsessive compulsive-spectrum disorders. The Sapap3 KO mouse shows a decrease in parvalbumin-positive (PV+) interneurons in the striatum. The relationship between the absence of SAPAP3 and the reduction in PV+ cells is still unknown, but it has been proposed that a cortical disinhibition in OCD patients due to GABAergic deficits could be linked to its pathogenesis. Therefore, we study, using a combination of in vitro and in vivo 2-photon experiments, the cortical GABAergic circuitry involving PV+ interneurons in the premotor area (M2). We have developed a Sapap3 null mouse line that express td-Tomato under control of the PV promoter. Preliminary results, using electrophysiological recording in brain slice preparation, show increased input resistance, decreased rheobase and increased firing frequency gain. All together indicate that PV+ interneurons are hyperexcitable. In vivo calcium imaging experiments in awake animals are in progress to confirm the hyperexcitability of PV+ neurons, and how the excitatory network is affected.

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PS2-31

# Area-specific patterns of convergent thalamic inputs to the mouse motor cortex

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A large region of the mouse dorsal and medial frontal isocortex is commonly labeled 'motor'. As such, this region is often compared with premotor and motor areas of the primate brain. However, the published histological and electrophysiological data in rodents provide ambiguous and often conflicting evidence for delineation of individual areas. Since multiple thalamic nuclei innervate the motor cortex, fine quantitative differences between mouse motor cortex regions in the thalamocortical input composition and/or intracortical distribution could provide an independent and consistent reference for area delineation, as well as for cross-species comparisons.

To map and quantify thalamus neurons innervating different motor cortex regions in the adult C57BL/6 mouse, we microinject in cortex retrograde tracers (Fast Blue and choleratoxin B conjugated with fluorochromes, CTB-Alexa) and use cytochrome oxidase activity to help in cortical layer and nuclei delineation. We calculate the percentage of labeled cells in each nucleus within all labeled cells in each case and compare then between cases. In subsequent experiments, the tangential/laminar convergence/divergence of these multiple pathways will be analyzed using micropopulation and single-cell anterograde labeling methods.

Our preliminary data show that, in all points explored, the most numerous sources of thalamic innervation comes from VM (ventromedial nuclei) and the complex VAL (ventral anterior-lateral nuclei), to a lesser extend from the posterior, intralaminar nuclei and the midline nuclei. Our data also reveal a remarkable heterogeneity in the set of nuclei whose projections converge at different points in the cortex, in addition to a complex topography within each nucleus. All of this supports the idea that the analysis of thalamic connections can provide valuable data for the consistent delineation of functional domains in the motor cortex of the mouse.

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PS2-32

# BBI: A Brain-Bacteria Interface to reveal and compute real-time changes in neuronal activity induced by bacterial presence

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The interaction of bacteria with various somatic cell types is an exciting emerging field. Despite the known effects of microbiota on the gut-brain axis, very little is known about the direct interactions that bacteria could have with neurons, both in terms of molecular mechanisms and information transfer. Here, we show how bacteria and neurons can be cultured together, and demonstrate a novel integrated platform that facilitates the analysis of neuronal-bacteria communication. Using optical (calcium signaling) real-time readouts, we show that neurons react to the nearby presence of bacteria, and that this response depends on the bacterial species and density. Thus, neurons sense the presence, type, and amount of bacteria, and can readily be interrogated in the living state to extract information about aspects of their microbial microenvironment. In addition, by fitting the bacterial-induced neuronal experimental data to a differential equation model, we ascertain Gompertzian parameters that can be used to predict neuronal response to bacteria presence as a function of time. Our proof-of-principle data in this highly tractable platform reveal crosstalk mediated by electrical and chemical signals and illustrate a novel example of cross-kingdom communication between highly diverse cell types. The ability to eavesdrop on information passing between these two very different levels of biological organization will facilitate insight into evolutionary cell biology and could impact the understanding of brain-bacteria communication for diagnosis of neuronal states in health and disease.

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PS2-33

# Electric fields modulation of epileptiform discharges in the cerebral cortex in vitro

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Transcranial direct current stimulation (tDCS) is a technique extensively used in the clinical realm to modulate cortical activity. tDCS has been suggested, among other applications, to induce suppression of epileptiform activity. However, the understanding of the mechanisms underlying tDCS neuromodulation over cortical dynamics is still limited. The goal here was to explore how DC fields modulate both pre-epileptic and epileptiform cortical activity in vitro, and their effects over the different components of cortical emergent activity.

We applied exogenous constant electric fields (EF) (between -5 and +5 V/m) to in vitro ferret cortical slices expressing slow oscillatory activity under control conditions and following the administration of bicuculline methiodide (BMI), a GABAA receptors antagonist. The blockade of GABAA inhibition resulted in the emergence of pre-epileptic discharges and, eventually, full-blown epileptiform discharges.

The frequency of epileptiform bursts was linearly modulated along the range of EFs used. The modulation was mainly exerted over the silent periods, that elongated for larger negative amplitude of the EFs, eventually reaching a complete suppression of epileptiform discharges. The duration of the bursts was hardly modulated by the EFs used, but their firing rate was. Interestingly, both positive and negative fields decreased firing rates, albeit probably by different mechanisms which will be discussed. As reported, the linear modulation of the frequency of bursts differs from the exponential modulation reported for the frequency of spontaneous (non-epileptic) Up states (D'Andola et al, bioRxiv, 246819, 2018), illustrating how the lack of inhibition decreases the range of flexibility of network responses.

Our results confirm that DC stimulation at the investigated intensities can modulate not only physiological but also disinhibited and more synchronous epileptiform activity, even reaching the silencing of full-blown epileptiform discharges. The present model might be useful to better understand the neuromodulation mechanisms of tDCS in the treatment of epilepsy patients.

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PS2-34

# Human α-synuclein overexpression in mouse serotonin neurons elicits a depressive phenotype: Focus on brain connectivity and synaptic density

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Anxiety and depression are the most prevalent neuropsychiatric disorders in Parkinson's disease (PD) population (≃50%), often preceding the appearance of motor symptoms. Neuropathological and neurochemical changes in the serotonin (5-HT) system occur during PD prodromal phase and contribute to a variety of non-motor symptoms. However, anxiety/depression brain circuits in PD are not known in detail. In this study, we hypothesized that synaptic impairments occur in the early stages of the disease onset before the neuronal cell loss. Dysregulating the synaptic junction would block neurotransmitter release, thus triggering a retrograde neurodegenerative process ending with neuronal cell loss by proceeding through the axons. We aimed to study whether synaptic density and functional connections are affected by α-synuclein accumulation in efferent brain regions from 5-HT raphe nuclei in the early stages of a depression/PD-like mouse model. We overexpressed human wild-type or A53T mutant α-synuclein (WTα-Syn and A53Tα-Syn, respectively) in 5-HT neurons using AAV vectors and two different synaptic markers, microtubule-associated protein 2 (MAP-2) and synaptic vesicle glycoprotein 2A (SV2A) were examined 4 and 8 weeks later. Mice overexpressing WTα-Syn showed progressive reductions of MAP-2 levels in different 5-HT-innervated cortices (e.g. prelimbic, infralimbic, cingulate and motor cortices), caudate putamen and different sub-fields of hippocampus. In parallel, WTα-Syn mice also showed an accumulation of SV2A protein in cingulate and motor cortices, and caudate-putamen. In addition, changes of MAP-2 and SV2A synaptic markers were also found in different 5-HT projection brain areas of A53Tα-Syn mice, although these changes were of greater magnitude. Brain functional activity was examined in these mice using rsfMRI and early gene zif628 expression. Altogether, these data suggest that changes in the density of MAP-2 and SV2A synaptic markers linked to α-synuclein-induced axonal pathology lead to reduced 5-HT neurotransmission evoking a depressive phenotype, and these effects precede neurodegeneration.

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PS2-35

# A neuroanatomical pathway for the integration of pheromonal and spatial information.

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Vomeronasal information plays a key role in rodents' individual recognition. This particular type of information could be integrated into the spatial context encoded in the hippocampus, thus constituting the neural substrate of the individual's integration into the cognitive map. Hence, pheromonal coding could represent the "who" component of episodic memory. In this work we describe an amygdalo-entorhino-hippocampal circuit from which vomeronasal stimuli may integrate into hippocampal processing. Through tract-tracing methods we demonstrate a glutamatergic reciprocal connection between the accessory olfactory bulbs and the posteromedial cortical amygdala (considered as the primary vomeronasal cortex), as a first potential nucleus for pheromonal information relay. To elucidate the connections from the vomeronasal amygdala to the dorsal hippocampus, the retrograde tracer FluoroGold was injected in the dorsal CA1 and the anterograde tracer TBDA (dextranamines labelled with biotin and rhodamine) in the primary vomeronasal cortex. Since no direct connection was found, we looked for areas where convergent retrogradely labelled cells and anterogradely labelled fibres were present. We found a restricted population of reelin-positive neurons retrogradely labelled in the dorsolateral entorhinal cortex layer II, where anterogradely labelled fibres with glutamatergic synaptic boutons were also present. To confirm this amygdalo-entorhinal pathway, retrograde tracer was injected in the dorsolateral entorhinal cortex. The results show that all the anteroposterior extent of the vomeronasal cortex projects to the dorsolateral entorhinal cortex, which in turn relays the pheromonal information to the dorsal CA1. Thus, we suggest that this circuit is the neural substrate of territorial behaviour in rodents, as well as the circuit allowing the integration of social and spatial information, that is, the "who" and "where" components of the episodic memory.

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PS2-36

# Rotations of prefrontal working memory representations to protect from task interference in a dual-task paradigm

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Recent studies involving complex working memory (WM) tasks or tasks with distracting inputs have suggested that stimulus representations before and after distractors are orthogonal, thus allowing for the protection of stimulus information from interferences. However, whether ”orthogonalization” is a general mechanism for WM preservation remains an open question. Moreover, the specific network mechanisms that could allow for such an orthogonalization are unknown. Here, we investigated orthogonalization as an instrument of WM control on calcium imaging data from the medial prefrontal cortex (mPFC) in a novel olfactory dual-task - the ultimate WM interference condition - in behaving mice. The dual-task consists of an outer delay-paired association task (DPA) combined with an inner Go-NoGo task. We studied how the representation of the sample stimulus of the DPA was affected by presenting the Go/NoGo cue of the inner task. Specifically, we examined how sample information is transformed during the delay period of the dual-task, focusing on inferring low-dimensional coding directions to evaluate orthogonality between WM representations at different epochs of the delay period of the outer task. We found a significant change in the directions representing DPA sample information before and after the Go/NoGo cue. This result indicates a rotation of the representation of sample information in the early delay period into an orthogonal representation in the late delay. To probe that mPFC plays an essential role in this mechanism, we investigated how memory storage was related to animal behavior. We found that memory rotation strengthens with learning. Altogether, our results suggest that rotation of WM representation in mPFC is a fundamental mechanism for maintaining WM information in the face of interfering distractor tasks. Finally, we give a mechanistic account of mPFC WM rotations in a network model of strongly recurrent neurons with low-rank connectivity structure.

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PS2-37

# Understanding the Potential Role of Sirtuin 2 on Aging: Consequences of SIRT2.3 Overexpression in Senescence

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Sirtuin 2 (SIRT2) has been associated to aging and age-related pathologies. Specifically, an age-dependent accumulation of isoform 3 of SIRT2 in the Central Nervous System has been demonstrated; however, no study has addressed the behavioral or molecular consequences that this could have on aging. In the present study, we have designed an adeno-associated virus vector (AAV-CAG-Sirt2.3-eGFP) for the overexpression of SIRT2.3 in the hippocampus of 2 month-old SAMR1 and SAMP8 mice. Our results show that the specific overexpression of this isoform does not induce significant behavioral or molecular effects at short or long term in the control strain. Only a tendency towards a worsening in the performance in acquisition phase of the Morris Water Maze was found in SAMP8 mice, together with a significant increase in the pro-inflammatory cytokine Il-1β. These results suggest that the age-related increase of SIRT2.3 found in the brain is not responsible for induction or prevention of senescence. Nevertheless, in combination with other risk factors, it could contribute to the progression of age-related processes. Understanding the specific role of SIRT2 on aging and the underlying molecular mechanisms is essential to design new and more successful therapies for the treatment of age-related diseases.

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PS2-38

# THE SOCIAL COMPONENT OF ENVIRONMENTAL ENRICHMENT IS A PRO-NEUROGENIC STIMULUS IN ADULT C57BL6 FEMALE MICE

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In rodents, the hippocampal dentate gyrus gives rise to newly generated dentate granule cells (DGCs) throughout life. This process, named adult hippocampal neurogenesis (AHN), converges in the functional integration of mature DGCs into the trisynaptic hippocampal circuit. Environmental enrichment (EE) is one of the most potent positive regulators of AHN. This paradigm includes the combination of three major stimulatory components, namely increased physical activity, constant cognitive stimulation, and higher social interaction. In this regard, the pro-neurogenic effects of physical activity and cognitive stimulation have been widely addressed in adult rodents. However, the pro-neurogenic potential of the social aspect of EE remains unexplored.

Here we tackled this question by studying the effects of a prolonged period of social enrichment (SE) in adult female C57BL6 mice. To this end, 7-week-old mice were housed in groups of 12 per cage for 8 weeks. These mice were compared with others housed under control housing (2–3 mice per cage) or EE (12 mice per cage plus running wheels and toys) conditions during the same period. We analysed the number and morphology of Doublecortin-expressing (DCX+) immature DGCs. Moreover, we used RGB retroviruses, which allow labelling three populations of newborn DGCs of different ages in the same mouse, to study DGC maturation, and performed and behavioural determinations.

Both SE and EE similarly increased the number and morphological and dendritic maturation of DCX+ immature neurons and newborn DGCs of different ages. Moreover, both manipulations increased exploratory behaviour in the Social Interaction test. Therefore, our data revealed the potent neurogenesis stimulating potential of SE in the absence of any further cognitive stimulation or increase in physical activity. Given that therapies based on increased physical activity may be strongly discouraged under certain pathological circumstances, our findings may be relevant in the context of enhancing AHN via physical activity-independent mechanisms.

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PS2-39

# Dealing with motherhood: Gene expression changes induced by pregnancy and lactation but not pup stimuli in the mouse medial amygdala

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During lactation, male-derived chemosensory signals produced by males induce aggression in adult female mice. However, pup-sensitized virgin females, which share pup care with the dams, are not aggressive against male intruders. The genetic mechanisms underlying the switch from attraction to aggression are still unknown. In this work, we investigate whether gene expression in the medial amygdala, a key nucleus in the integration of chemosensory and hormonal information, differs between aggressive lactating females and non-aggressive pup-sensitized virgin females. To do so, we performed a RNA-sequencing study. Our data reveals that 197 genes are upregulated in dams, among which we find genes encoding hormones such as prolactin, growth hormone, or follicle-stimulating hormone, neuropeptides such as galanin, oxytocin and proopiomelanocortin, and genes related to catecholaminergic and cholinergic neurotransmission. By contrast, 99 genes are downregulated in dams, including those encoding inhibins and transcription factors of the Fos and early growth response families. The gene set analysis revealed numerous Gene Ontology functional groups with higher expression in dams than in pup-sensitized virgin females, including the group of genes related with the regulation of the Jak/Stat cascade and the negative regulation of the ERK1 and ERK2 cascade. Interestingly, we found several genes encoding olfactory and vomeronasal receptors expressed in the medial amygdala, although no differences in expression were observed between dams and virgins. Our results reveal many gene expression changes in the medial amygdala, previously unknown, which may underlie the behavioural changes observed in lactating females in relation to conspecific males.

KEY WORDS: vomeronasal amygdala, RNA-Sequencing, aggression, prolactin, transcriptome, maternal behaviours, females.

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PS2-41

# Galanin and neuropeptide Y interactions linked to neuronal precursor cells of the dentate gyrus in the hippocampus. Role in depression and cognitive impairment.

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Galanin (GAL) interacts with Neuropeptide Y Y1 receptors (NPYY1R) in several regions of the central nervous system associated with mood and motivation, through GAL receptor 2 and NPYY1 receptor 1 (GALR2/NPYY1R) heterodimers. The current work is to evaluate GALR2 and NPYY1R interactions concerning newborn cell proliferation in the ventral and dorsal hippocampal Dentate Gyrus.

Rats (n = 6-8 per group) were randomly assigned to the groups. Each group received i.c.v. injections of artificial Cerebro Spinal Fluid (aCSF), GAL or NPYY1R agonist [Leu31,Pro34]NPY alone or in combination and 24 h later rats were subjected to a 5-min swimming session (test). A different set of rats received ip injections of BrdU 50mg/Kg at 2 and 4 hours after icv injections. 24 hours later brains collected for immunostaining to evaluate cell proliferation.

We observed that the icv injection of GAL and NPYY1R agonist significantly enhanced the decrease in the immobility and the increase in the swimming behavior compared with the NPYY1R agonist alone. Furthermore, GALR2 is involved in this GALR/NPYY1R interaction, since the presence of the GALR2 antagonist M871 counteracted all the parameters. In parallel, coadministration of GAL and NPYY1R agonist increased BrdU-labeled cells located in the SGZ compared with aCSF, GAL and the NPYY1R group. Similar results were observed in dorsal hippocampus.

Our results may provide the basis for the development of heterobivalent agonist pharmacophores, targeting GALR2/NPYY1R heteromers, especially in the neuronal precursor cells of the dentate gyrus in the hippocampus for the novel treatment of depression or cognitive impairments.

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PS2-42

# INDIVIDUAL VARIATION IN DROSOPHILA MELANOGASTER IMPACTS FEEDING BEHAVIOR

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In front of a stimuli organisms from the same species tend to behave apparently similar, tending to show similar types of choices, but some aspects of the behavior can display huge variability among individuals. That phenotypic variation emerges from the combination of gene function and developmental factors, including experience, that may impact on the survival of the organisms in the environment. A behavior of particular interest is the ability of animals to differentiate properly the nutritious from the poisonous food as it is key for their survival. Interestingly, feeding behavior shows great variability between individuals and in addition, the behavioral responses are clear and easy to measure, making it an ideal model where to study the genetic basis of animal personality and stochastic behavior. For the present study we have used a collection of inbred lines, Global Diversity Lines (GDL), to address the genetic basis of feeding variation among individuals by analyzing the feeding microstructure at individual and collective context with different behavior assays. We have found that variation among GDL lines from the same population is lower than between GDL lines from different populations. Further, there are specific lines that show higher sensitivity to sucrose measured with Proboscis Extension Reflex (PER) which is also correlated with higher feeding activity according to two-choice feeding assays (FlyPad). These findings suggest that there is a positive correlation between sensitivity to sucrose and two-choice activity, and that specific genetic background is responsible for this behavior, which vary more between populations than within lines from the same population.

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PS2-43

# Relevance of metalloproteinase-9 in depression: a study in transgenic animal models

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Major depressive disorder (MDD) is one of the main causes of disability worldwide. Its etiopathology is still unknown, but several hypotheses have been proposed. The matrix metalloproteinase 9 (MMP-9) is overexpressed in plasma of depressive patients and its levels are restored after chronic treatment with antidepressant drugs. Therefore, the aim of this work is to characterize the behavioural phenotype of transgenic MMP-9 mice in tests related to anxiety/depression-like behaviour.

In this work, we used MMP-9 knockout (MMP-9 KO) and MMP-9 overexpressing (MMP-9 OE) male and female mice, and their corresponding wild types (WT) counterparts, 2-3 months old. To characterize the transgenic mice phenotype, a battery of depressive- (social interaction and tail suspension test) and anxiety- (open field and novelty-suppressed feeding test) like behavioural tests were assessed.

On the one hand, MMP-9 KO male mice spent more time, both, in the centre of the open field test and the interaction zone of the social interaction test than the WT male mice. MMP-9 KO female mice spent less time in the centre of the open field and presented less immobility time in the tail suspension test. On the other hand, MMP-9 OE male and female mice had an increased latency to feeding than their WT counterparts in the novelty-suppressed feeding test. Moreover, MMP-9 OE female mice spent more time in the centre of the open field test.

In conclusion, the levels of MMP-9 had a different impact in the behavioural phenotype sex-dependent. MMP-9 KO mice do not present a depressive-like phenotype. Nevertheless, MMP-9 KO male mice have less innate anxiety, while females are more anxious. In contrast, MMP-9 OE mice have a depressive-like phenotype, while MMP-9 OE male mice present increased innate anxiety and MMP-9 OE females show less innate anxiety.

PS2-44

# Effects of chronic CB1 receptor agonist ACEA in a mouse model of Alzheimer's Disease.

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Alzheimer's disease (AD) is characterized by the brain presence of amyloid beta plaques, increased amyloid precursor protein (APP) and neurofibrillary tangles and courses with progressive behavioural alterations including cognitive and socio-affective dysfunctions. Although AD cause a huge impact on patient daily life representing the most common form of dementia, current treatments for AD only provide symptomatic relief. There is the need to better understand the brain mechanisms leading to this devastating disease. In this sense, alterations of the endocannabinoid system (ECS) have been found in animal models and human patients, and its modulation has been proposed as a new therapeutic avenue for the treatment of this disease.

In this study, we combined the APP/PS1 mouse model of AD with a pharmacological intervention at 3 months of age using the CB1 receptor cannabinoid agonist ACEA under a regimen of 21 consecutive days. At 4, 6, 9 and 12 months of age we performed a complete sex- and age-dependent behavioural characterization (cognition, social-related behaviours, depressive and anxiety-like states). In addition, we also performed an age-, sex-, brain-region- and cell-type specific characterization of the ECS and some related mechanisms.

APP/PS1 male mice showed cognitive deficits from 6 months of age that are maintained until 12 months of age. This cognitive impairment was not observed in APP/PS1 female mice. Interestingly, ACEA chronic treatment reversed the cognitive alterations observed in male mice. In addition, we have found sex- and brain region-dependent alterations on different ECS components at asymptomatic stages (3 months of age).

Altogether, this project provides compelling evidence on the importance of sex, age and brain locations when studying a complex brain disorder such as AD. Indeed, our results suggest the presence of gender differences in AD and reaffirm that cannabinoid drugs could be a beneficial therapeutic avenue for this brain disorder.

PS2-45

# The associative striatum mediates flexible expectation-based choice biases

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Recent actions and their outcomes can generate expectations that guide upcoming choices, but the underlying neural circuits have yet to be specified. We hypothesized that the associative striatum (i.e. DMS) is well positioned to support such cognitive function, and hence designed a task and manipulation that would allow us to differentiate it from the role of striatum in motor control. To promote the use of expectations, we used a two-alternative auditory discrimination task with serial correlations in the stimulus sequence. A generalized linear model confirmed that rats leverage on the recent history of rewarded responses to estimate the next correct choice when evidence is ambiguous, referred to as the transition bias. We virally expressed the opsin stGtACR2 in DMS projection neurons to silence their somata in the millisecond scale. Bilateral photostimulation during the inter-trial interval (ITI; ~ 20% trials), i.e. before stimulus onset, markedly reduced the transition bias compared with light-off trials. In contrast, ITI inhibition had no effect after an error response when rats temporarily waived trial history, consistent with a cognitive effect of inhibition. Notably, ITI inhibition increased or decreased response accuracy depending on the congruence of the trial with the serial correlation, but independently of response time. Strikingly, unilateral ITI inhibition was equally effective at ablating transition bias for ipsi- and contralateral responses, clearly departing from the ipsiversive effect of unilateral inhibition during action selection. Together, our new findings change the current view of the DMS, and provide a starting point to dissect the circuits subserving rule-based expectations.

PS2-46

# Modulation of gut microbiota as a therapeutic approach to improve behavioural deficits in a mouse model of Down syndrome.

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Proper social interaction with others, conserved cognitive abilities and a good motor coordination are crucial functions for our everyday life. Deficits in all these behavioural processes have been described in many neurodevelopmental disorders such as Down syndrome (DS). Although most of these abnormalities have a more profound impact in the daily functioning, more attention should be given to find potential therapeutic strategies to diminish their consequences. Several studies point the gut microbiota to play an active role in cognitive functions and social domains through the regulation of the gut-brain-axis (GBA). For this reason, we hypothesize that some cognitive and social alterations in DS individuals may be modified by modulating the GBA. In this work, we supplemented Ts65Dn mice, an accepted mouse model of DS, with a synbiotic treatment before gestation and, at 8 weeks old mice, we performed several behavioural paradigms to assess motor coordination (beam walking), cognitive functions (novel object recognition) and social functions using the three-chamber task and the affective state discrimination test (ASD). Our results suggest that Ts65Dn mice present sex-dependent changes in sociability and that a synbiotic treatment is able to reverse these phenotypes. Interestingly, we also show for the first time that Ts65Dn mice present a deficit in emotional recognition in the ASD test, since they are not able to discriminate between a negatively affected mouse and a neutral mouse. Strikingly, this phenotype can be rescued with synbiotic supplementation only in male mice. Overall, this study showed novel behavioural phenotypes in a mouse model of DS and suggests that the dietary modulation of the GBA could emerge as a promising therapeutic strategy to improve behavioural disturbances in DS.

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PS2-47

# Sub-chronic peripheral cannabinoid type-1 receptor blockade enhances cognitive performance in naïve mice and in a model of fragile X syndrome

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Memory is a physiological function that allows encoding and storing information over time, to be later retrieved for specific purposes. Intellectual disability disorders such as fragile X syndrome, show in most cases deficits in learning and memory performance. Fragile X syndrome is a rare disorder derived from the repression of the FMR1 gene in humans, which has been modeled in mice by knocking out the Fmr1 gene (Fmr1 KO). Our group has previously demonstrated that the peripheral cannabinoid type-1 receptor (CB1R) participates in memory modulation. Thus, peripheral CB1R activation occurs under acute stress conditions reducing memory persistence, while acute peripheral CB1R blockade enhances memory persistence. We now evaluated the behavioral, cellular and molecular outcome of a sub-chronic blockade of peripheral CB1Rs in naïve mice and in Fmr1 KO mice. We found that sub-chronic (7 d) administration of the peripherally restricted CB1R antagonist AM6545 shows in naïve mice a mnemonic effect measured in the novel object-recognition memory test (NORT). No changes in the proliferative marker Ki67 were observed in the subgranular zone of the dentate gyrus, while AM6545 sub-chronic treatment induced changes in hippocampal dendritic spine morphology driving an enhancement of mature spines. Sub-chronic peripheral CB1R blockade also occluded long-term potentiation in CA3-CA1 hippocampal synapses and increased the hippocampal expression of Bdnf and Ngf neurotrophic factors. Interestingly, executive function facilitation was observed after sub-chronic AM6545 administration in naïve mice. In Fmr1 KO mice, sub-chronic AM6545 treatment prevented NORT deficits and normalized aberrant mGluR5-dependent long-term depression and dendritic spine alterations. Altogether, our results suggest that the peripheral CB1R contributes to the modulation of memory persistence and hippocampal synaptic plasticity both in naïve mice and in a model of fragile X syndrome, mimicking the effects previously observed of systemic approaches reducing CB1R function.

PS2-48

# Neuraminidase-induced neuroinflammation causes anxiety and microgliosis in the amygdala

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An intracerebroventricular (ICV) injection of neuraminidase (NA) within the lateral ventricles originates an acute event of neuroinflammation, which is solved to a great extent after two weeks. Recently, neurological problems or behavioral alterations have been associated with neuroinflammation. Although the majority of them fade along with inflammation resolution, the possibility of long-term sequelae should be taken into consideration. Thus, we aimed to explore if NA-induced neuroinflammation provokes behavioral or neurological disturbances at medium (2 weeks) and long (10 weeks) term. Initially, rats were ICV injected with NA or saline. Two or 10 weeks later they were made to perform a series of neurological tests and behavioral evaluations (open field test). The neuroinflammation status of the brain was studied by immunohistochemistry and qPCR. While no neurological alterations were found, the open field test revealed an increased anxiety state 2 weeks after NA administration, which was not observed after 10 weeks. In accordance with this behavioral findings, an overexpression of the molecular pattern receptor TLR4 was revealed by qPCR in hypothalamic tissue in NA treated animals after 2 weeks of ICV, but not after 10 weeks. Moreover, histological studies showed a microgliosis in the amygdala of NA injected rats 2 weeks post-ICV, as well as a slightly activated state evidenced by morphometric parameters of these cells. These histological findings were not present 10 weeks after the ICV injection. These results suggest that NA-induced neuroinflammation might cause anxiety, with no neurological manifestations, in the medium term, along with a mild microglial activation in amygdala. Such symptoms seem to revert, as they were not detected 10 weeks after NA administration.

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PS2-49

# Evoked neural population activity during static and dynamic visual stimuli recognition: a comparative study based on intracranial EEG

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It takes a fraction of a second to recognize a person even when seen under strikingly different conditions. However, how such a robust, high-level representation is achieved by neurons in the human brain is still unclear. In particular, the way that neurons encode different percepts is one of the most intriguing questions in neuroscience and has to a large extent been addressed in poorly realistic experimental conditions. In this work we study the activity of neural populations in humans during conscious perception of realistic stimuli. To this aim, we evoke brain responses to static and time-varying visual representations of consciously perceived faces and characterize the differences between their evoked brain responses.

To address the above question, we designed task paradigms and developed a methodological pipeline based on human intracranial recordings (iEEG) to localize and quantify time-varying brain responses to consciously perceived stimuli of static and dynamic modality. Our initial analysis in 3 subjects during static face recognition revealed significant brain responses in regions from occipital, temporo-parietal and frontal lobe, thus characterizing the sequential engagement of key areas along the visual processing pathway. Moreover, when faces were viewed within a dynamic context, known high-frequency responses to recognized concepts [1] significantly diminished their intensity in specific regions of the medial temporal lobe, suggesting that (more) ecological stimuli might be differentially processed in brain areas traditionally associated with episodic memory.

Overall, this work systematizes existing methodology to localize neural population activity measured with intracranial EEG during cognitive tasks and explores the specificities of these neural activations when conscious recognition takes place under a more realistic setting than that of static object viewing.

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PS2-50

# Epileptogenic biomarkers based on combined power activation and connectivity of iEEG signals

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The only effective treatment of pharmacoresistant epileptic patients relies nowadays on surgery. Over the last decade many computational approaches have attempted to characterize the epileptogenicity of brain signals recorded with either scalp or intracranial EEG (iEEG) to localize the seizure focus and improve pre-surgical planning. Most of these contributions with iEEG have estimated seizure-driven power activations, while connectivity measures have been applied in scalp EEG studies and shown to improve localization in this modality. However, the interplay between power and connectivity features in iEEG with regard to seizure focus localization has not been thoroughly addressed. As a result, a few questions arise in this context: How redundant are connectivity measures with respect to power activations of iEEG signals during pre-seizure and seizure periods? How much information do linear connectivity measures add to power activations to improve seizure focus localization?

For the same cohort of patients analyzed in [1], we characterized the level of redundancy of linear connectivity measures with respect to power activations during seizures and pre-seizure periods at different frequency bands. For almost all patients, the connectivity strength (measured via Pearson correlation) was in general highly redundant with respect to the power activations when evaluated across recording sites during seizure epochs. This level of redundancy was always manifested at the broad frequency spectrum (1-150Hz) and was localized at specific frequency bands for each patient. The level of redundancy was significantly higher during seizure than pre-ictal epochs. This indicates that basic non-directional linear connectivity is highly influenced by power coactivations that might be caused by either physiological mechanisms and/or by statistical biases of the connectivity measures. Overall, these preliminary results question the addition of linear connectivity measures to improve current power-based algorithms for seizure focus localization.

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PS2-51

# Finding Useful Biomechanics Markers as Functional Correlates of the Eyelid Movements

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Most studies on eyelid movements focus on the determination of physiological variables and parameters such as latencies, peaks, or areas. Nonetheless, very few are dedicated to revealing significant information on the anatomical-functional conglomerate (active and passive contributions of muscle fibers, ligaments, and other connective tissues) that support the biomechanics of the eyelid motor system and, therefore, the palpebral kinematics. This study aims to design and develop an analytical-experimental approach that integrates in a single formulation the phenomenological and computational modeling of eyelid movements, in the general context of a paradigm of classic conditioning of the blink reflex. A relevant aspect of our approach was that modeling of the angular displacement of the eyelid was carried out in relation to the force component of the orbiculari oculi muscle mainly in the closing phase and in the first stage of the opening phase, which informs us of a series of biomechanical parameters useful for the exhaustive control of the eyelid kinematics. By simulation, the model proposed here also characterized the dynamics of the antagonist levator palpebrae muscle, resulting on a more realistic modelling of the second stage of the opening phase. The results showed that there were a significant number of optimization trials (search of verisimilitude between the observed experimental recording and the simulated theoretical solution for the palpebral position) which were classified as good or excellent (67.2%), according to our Versatile Interface for Optical Fitting of Eyelid Kinematics (VIOFEK). Finally, it is important to point out that there are several possible clinical applications of this analytical-experimental approach. This model could help a more objective clinical exploration of neuromuscular disorders (facial nerve paralysis), pathologies with prevalence of eyelid dysfunctions (ptosis, blepharospasm and hemifacial spasm) and follow-up after eyelid surgery.

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PS2-52

# Information transmission in delay-coupled neuronal circuits in the presence of a relay population

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Synchronization between neuronal populations is hypothesized to play a crucial role in the communication between brain networks. The binding of features, or the association of computations occurring in spatially segregated areas, is supposed to take place when a stable synchronization between cortical areas occurs. While a direct cortico-cortical connection typically fails to support this mechanism, the participation of a third area, a relay element, mediating in the communication was proposed to overcome this limitation. Among the different structures that could play the role of coordination during the binding process, the thalamus is the best placed region to carry out this task.

We studied how information flows in a canonical motif that mimics a cortico-thalamo-cortical circuit composed by three mutually coupled neuronal populations (called V-motif), Through extensive numerical simulations, we found that the amount of information transferred between the oscillating neuronal populations is determined by the connection delay and the mismatch in their oscillation frequencies (detuning). While the transmission from a cortical population is mostly restricted to positive detuning, transmission from the relay (thalamic) population to the cortical populations is robust for a broad range of detuning values, including negative values, while permitting feedback communication from the cortex at high frequencies, thus supporting robust bottom-up and top-down interaction. Interestingly, the addition of a cortico-cortical bidirectional connection to the V-motif (C- motif) expands the dynamics of the system with distinct operation modes. While overall transmission efficiency is decreased, new communication channels establish cortico-thalamo-cortical association loops.

Switching between operation modes depends on the synaptic strength of the cortico-cortical connections. Our results support a role of the transthalamic V-motif in the binding of spatially segregated cortical computations, suggesting an important regulatory role of the direct cortico-cortical connection

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PS2-53

# Astrocytic calcium dynamics in multiple sclerosis: regulation by CB1 receptors

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Multiple sclerosis (MS) is a chronic demyelinating disease initiated by pathogenic immune responses against myelin followed by a broader inflammatory and neurodegenerative process. Astrocytes physiologically respond to endocannabinoids and other synaptically released neurotransmitters with cytosolic Ca2+ elevations that engage intracellular signaling and fine-tune intercellular communication. MS induces a pronounced transformation of astroglial cells whereby they acquire a variety of disease-promoting functions. In particular, accumulating evidence supports the existence of a subset of neurotoxic reactive astrocytes that exhibit transcriptional programs destructive to synapses and oligodendrocytes in response to pro-inflammatory signals. Aberrant Ca2+ signals in reactive astrocytes are closely related to disease severity in a number of neurological disorders. However, the Ca2+ handling properties of astrocytes in the context of autoimmune demyelination remain to be investigated.

In this study we analyzed astrocyte Ca2+ dynamics and their modulation by CB1 receptors in the experimental autoimmune encephalomyelitis (EAE) mouse model of MS as well as in neurotoxic astrocytes induced in vitro. Systemic administration of Δ9-THC increased the amplitude of astrocytic Ca2+ transients in the somatosensory cortex of freely moving mice carrying astroglial GCaMP6. Cannabinoid-induced increase of astroglial Ca2+ levels was mediated by the population of CB1 receptors present astrocytes as determined using GFAP-CB1-KO conditional mutant mice. EAE induced a shift in spontaneous astrocytic Ca2+ activity that correlated to disease symptomatology and attenuated Ca2+ responses mediated by Δ9-THC. Astrocytes purified during acute EAE exhibited deregulated gene expression of several membrane receptors coupled to intracellular Ca2+ regulation as well as changes affecting Ca2+ signaling/homeostatic toolkits. These observations were partially mimicked by neurotoxic activation of cultured astrocytes and associated to aberrant cytosolic Ca2+ responses by ATP and glutamate. Our results suggest deficits in spontaneous and pharmacologically induced astrocytic Ca2+ activity during autoimmune demyelination that may reflect and/or contribute to MS disease severity.

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PS2-54

# Amyloid propagation in a sporadic model of Alzheimer disease

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- Most age-associated neurodegenerative disorders involve the aggregation of specific proteins within the nervous system, as occurs in Alzheimer's disease (AD). Recent evidence indicates that Aβ can misfold and aggregate into seeds that structurally corrupt native proteins, mimicking a prion-like process of template protein corruption or seeding. In fact, studies in FAD-based animal models show that Aβ deposition and cerebral amyloid angiopathy may be induced by intracerebral infusion of brain extracts from AD patients or from aged APP-transgenic mice. These studies have shown that the characteristic of both the seeding agent and the host influence the pathologic signature of the Aβ seeds. In this regard, the majority of the Aβ-seeding studies have been done in APP-transgenic animal models that overproduce APP and/or Aβ. However, it remains to be elucidated whether Aβ deposition can be induced by Aβ seeds in an animal model that does not overexpress APP and produces wild type human Aβ and if these aggregates are similar to the human condition.
- Here, we used an innovative animal model to better understand the amyloidogenic events that occur in the sporadic form of the disease. Our model, termed hAβ-KI, expresses wild-type human Aβ under the control of the endogenous mouse APP gene. Thus, amyloid seeds from AD patients (stage C for amyloid) from the Alzheimer's Disease Research Center (ADRC) at UCI were administered into 7-8-month-old hAβ-KI and as positive controls 3xTg-AD mice were employed.
- Our findings demonstrated that amyloid seeds differentially occur in 3xTg-AD and hAb-KI mice and these aggregates are developed earlier in the familial model, 3xTg-AD mice.
- These results suggest that multiple factors such as the seed, recipient model and time are critical factors that can modulate the amyloid pathology onset and progression. Thus, more profound understanding these factors will provide key insight on how amyloid pathology progress in AD.

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PS2-55

# Effect of the Src inhibitory peptide TAT-Cx43$_{266-283}$ on neural stem cells with EGFR overexpression or EGFRvIII mutation

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Glioblastomas are one of the most malignant tumours worldwide. Among the causes of such malignancy is a subpopulation of tumour cells with stem cell properties known as Glioma Stem Cells (GSCs). These cells are resistant to standard treatments, such as temozolomide, which causes tumour recurrence. Several studies have proposed Neural Stem Cells (NSCs) from the subventricular zone (SVZ) as a possible origin for GSCs. The transition of NSCs to GSCs frequently concurs with epidermal growth factor receptor (EGFR) overexpression or mutations, such as EGFRvIII. Our group designed a cell penetrating peptide based on connexin43 (TAT-Cx43$_{266-283}$) that inhibits the activity of the oncoprotein c-Src and therefore targets GSCs, increasing survival rates in glioma-bearing mice. Because Src is involved in EGFR signaling, we aimed to explore the effect of TAT-Cx43$_{266-283}$ in the transition of NSCs to GSCs. For this purpose, we analysed the cell growth of SVZ NSCs (Control-NSCs), NSCs with EGFR amplification (EGFRwt-NSCs) and NSCs with the mutant EGFRvIII (EGFRvIII-NSCs). Our results show that TAT-Cx43$_{266-283}$ specifically inhibited the growth of EGFRwt-NSCs and EGFRvIII-NSCs, without significant effects in Control-NSCs. Importantly, we found that temozolomide and other control peptides did not affect the cell growth of any of these NSCs. To gain insight into the mechanism involved in the effect of TAT-Cx43$_{266-283}$, we analysed the EGFR signaling pathway by Western blot. Our preliminary results show that TAT-Cx43$_{266-283}$ decreased the activity of EGFR and EGFRvIII, as well as c-Src activity. So far, our results indicate that TAT-Cx43$_{266-283}$ impairs EGFR signaling pathway with the subsequent reduction in the proliferation and survival of NSCs that overexpress or exhibit mutations in EGFR. These results stress the relevance of TAT-Cx43$_{266-283}$ as a future therapy against glioblastoma, alone or in combination with temozolomide or other treatments that do not target stem cells with EGFR alterations.

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# PS2-56

## Microglia are key regulators of the innate anti-tumoural response in late adulthood

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Glioblastoma and metastatic brain tumours are incurable diseases with short life expectancy. Microglia are the resident macrophages of the Central Nervous System, accounting for up to the 30% of the total tumour mass. They show an immune suppressive response supporting cancer growth. In general, microglia can adopt different states of polarisation, although the reasons of the phenotypic switch are not fully understood. However, it is known that cancer cells drive the phenotype of surrounding immune cells into a pro-tumoural state.

In turn, during aging, microglia evolve into a 'priming' state with clear pro-inflammatory features. This inflammatory phenotype has been widely associated with the onset of different neurodegenerative diseases. Nevertheless, in the context of brain tumours, we hypothesise that the incidence of brain tumours at the old age is significantly reduced mainly because of the pro-inflammatory microenvironment generated by aged-microglia.

To prove that, we have used in vitro mouse models of microglia (BV-2), glioblastoma (GL261) and breast cancer brain metastasis (EO771). We have also performed in vivo studies to quantify the tumour burden in aged mice (18 and 24 months) compared with young mice (3 months).

We show by qPCR, western blot and immunohistochemistry how senescent microglial cells develop a strong pro-inflammatory response once exposed to tumour-conditioned media. In the same vein, we have seen a significantly reduction of the tumour size in aged mice. Key pro-inflammatory biomarkers (e.g. iNOS and TNFα) were significantly up-regulated not just in the tumour microenvironment but also in the tumour-associated aged microglia.

To the best of our knowledge, this is the first empirical demonstration of how senescent microglial cells are associated with the reduction of brain tumours growth. Unraveling the molecular mechanisms behind the pro-inflammatory activation of senescent microglial cells could lead us to potential new treatments to modulate the immune response against brain tumours.

PS2-57

# ENDO-LYSOSOMAL DISRUPTION DRIVES MICROGLIAL PHAGOCYTOSIS DYSFUNCTION IN STROKE

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Microglial phagocytosis of apoptotic cells is an essential process to maintain tissue homeostasis and avoid the spillover of the cytotoxic content that results from the cell death induced by excitotoxicity and/or inflammation. We have shown that microglial phagocytosis is chronically impaired in models of neurodegenerative diseases such as epilepsy and stroke, where microglial phagocytosis is blocked as early as 6h after transient Medial Cerebral Artery occlusion (tMCAo), a model of stroke. We hypothesize that microglial phagocytosis impairment in tMCAO was related to an energetic failure and used different in vitro systems to test the role of oxygen and nutrient deprivation (OND). To assess the effect of OND on phagocytosis we first used hippocampal organotypic slices and observed a similar defect in apoptotic cell phagocytosis, which was related to a reduced microglial surveillance and process motility by 2-photon microscopy, likely related to the generalized energetic failure in stroke. The OND-induced phagocytosis reduction rapidly recovered after reperfusion suggesting that, in addition to the acute energetic failure, a more complex mechanism is responsible for the long-term impairment of phagocytosis found in tMCAo mice. We then treated primary microglial cultures with OND and observed phagocytosis deficits, in particular, a reduced degradation of apoptotic cells. This reduction was related to an increased lysosomal pH, possibly as a consequence of alterations in energy-dependent proton pumps that lead to a deficient enzymatic activity. The energetic dysfunction not only affected phagocytosis but also autophagy, another endolysosomal pathway. We assessed autophagy using electron microscopy and found an increase in autophagy-like vesicles, presumably due to stalled autophagosomes related to a deficient lysosomal degradation. To revert the phagocytosis impairment, we tested the autophagy inductor rapamycin, both in vitro and in vivo, to restore the autophagy flux and the altered endolysosomal pathway, and hence, recover the phagocytic activity. Thus, the microglial phagocytic potential opens a novel approach to accelerate the recovery of the ischemic brain by harnessing microglial phagocytosis of apoptotic cells through the stimulation of autophagy.

PS2-58

# Generation of GRIN-related disorders Zebrafish models library for endophenotypic characterization and pharmacological screening

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NMDA ionotropic glutamate receptors play pivotal roles in synaptic development, plasticity, neural survival, and cognition. Recent advances on Next-Generation Sequencing revealed the association of de novo mutations affecting GRIN genes (encoding GluN subunits of the NMDAR) with neurodevelopmental disorders, so-called GRIN-related disorders (GRD) or Grinpathies. GRD is a rare condition with a clinical spectrum dictated by both the affected GRIN gene and the functional outcomes of the mutated residue/s, primarily affecting glutamatergic neurotransmission and causing synaptopathies. Accordingly, generation of an in vivo library is required, in order to cover the genetic aetiologies underlying GRD phenotypes, to delineate the neurological alterations and ultimately to identify personalized therapeutic approaches for GRDs. In the context of GRD, zebrafish appears as an optimal animal model, since it provides several advantages from biomedical and industrial points of view (e.g. fast generation of genetic models, multidimensional phenotyping and reliable in vivo pharmacological screening).

To address this objective, CRISPR-Cas9-based genome editing technology has been applied for the obtention of knockout models of Zebrafish paralogous GRIN1, GRIN2A and GRIN2B genes. Single mutant larvae showed no effect on survival rate, and allowed to define the spatio-temporal expression pattern of Grin genes in Zebrafish larvae. Interestingly, in addition to a prominent expression in the brain, NMDAR subunits were also detected in peripheric organs (e.g. heart, intestine). Currently, phenotypic assessment is being performed in pharmacological acute GRD models that revealed the presence of both behavioural and motor endophenotypes. In the short term, the comprehensive phenotyping of Zebra-GRIN models will allow to define GRD-like alterations and, importantly, to evaluate the therapeutic efficacy of repurposed and EMA-approved putative NMDAR allosteric modulators, to ultimately allow personalized therapies for GRD patients.

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PS2-59

# High-fat feeding shifts the gut microbiome and accelerates retinal degeneration in retinitis pigmentosa mice

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High-fat diets (HFD) can lead to shifts in the gut microbiota and metabolic alterations and have been associated with increased risk of cognitive dysfunction. Here, we analyze the effects of a HFD on the gut microbiome and the neurodegenerative process in an animal model of retinitis pigmentosa (RP). Wild-type C57BL/6J and rd10 mutant (RP) mice were fed either with normal chow (5.5% fat kcal) or with a HFD (61.6% fat kcal) for two weeks after weaning (P19). At the endpoint, retinal function was evaluated by optomotor test and electroretinography. The structure and integrity of the retina were studied by immunohistochemistry. The gut microbiome was analyzed by 16S rRNA gene sequencing. Rd10 mice showed diminished retinal responsiveness and visual acuity, loss of photoreceptor rows, and morphologic anomalies in the remaining photoreceptor cells, compared to C57BL/6J mice. Photoreceptor degeneration was associated to proliferation of microglial cells and reactive gliosis of Müller cells. The gut microbiome analysis revealed differences between healthy and dystrophic mice in alpha and beta diversity at the genera, species and amplicon sequence variants levels. HFD consumption produced significant dysbiosis in the gut microbiome of both wild-type and mutant mice, increasing potentially pro-inflammatory bacteria. In wild-type mice, HFD consumption did not affect retinal structure and function. But HFD intake by rd10 mice decreased retinal responsiveness and visual acuity, increased photoreceptor degeneration, and exacerbated microglial cell activation and Müller cell gliosis. Also, HFD consumption enhanced the expression of inflammatory and cell death markers in rd10 retinas. In conclusion, retinal degeneration in retinitis pigmentosa is linked to significant changes in the gut microbiome, which can be altered by the diet, leading to deterioration of the disease. The results suggest that increased consumption of fat could aggravate the progression of the disease in patients with retinal degenerative disorders. MINECOFEDER-BFU2015-67139-R, MICIINN-FEDER PID2019-106230RB-I00, RETICS-FEDER-RD16/0008/0016, IDIFEDER/2017/064

PS2-60

# Activating epigenetic modifications are upregulated in the post-mortem brain of schizophrenia subjects: Effects of antipsychotic treatment

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Susceptibility to develop schizophrenia (SZ) is determined by complex interactions between genes and environment. Environmental risk factors may exert their negative effects at critical stages of brain development, possibly via epigenetic mechanisms. While most studies evaluated gene-selective epigenetic modifications, few studies reported SZ-associated alterations affecting epigenetic mechanisms globally. Here, we evaluated the global expression of histone posttranslational modifications (HPTM) in a case-control cohort of SZ subjects.

Dorsolateral prefrontal cortex samples of SZ subjects and age-, sex-, and post-mortem delay- matched controls were obtained at autopsies performed at the Basque Institute of Legal Medicine. SZ subjects were divided into antipsychotic treated (AP-treated) or antipsychotic free (AP-free) groups, according to blood toxicological data at the time of death. For this study, cortical amounts of gene expression activating (H3K9ac, H3K27ac, H3K4me3 and H4K16ac), and repressing (H3K9me3, H3K27me3 and H4K20me3) HPTM were quantified by Western Blot.

H3K9ac (+42%, $p<0.01$), H3K27ac (+28%, $p<0.05$) and H3K4me3 (+24%, $p<0.05$) were significantly increased in SZ subjects, compared to matched controls. Cortical immunodensities of all other HPTM did not show significant differences between SZ subjects and controls. Subgroup analyses in AP-free and AP-treated SZ subjects revealed that H3K27ac and H3K4me3 were specifically increased in AP-treated group. Pearson's correlation analyses showed overall positive associations between activating and, separately, between repressing HPTM. The expression of activating H3K4me3 also correlated with that of repressing H3K27me3.

In conclusion, upregulation of H3K9ac, H3K27ac and H3K4me3 may be associated with globally increased gene expression in SZ. AP treatment might enhance H3K27ac and H3K4me3 levels. Future studies should clarify whether the observed upregulation of cortical H3K27ac and H3K4me3 might be part of the mechanism of action of AP drugs, or due to a specific mechanism in SZ brain. Finally, the overall correlations between the HPTM species suggests that epigenetic mechanisms are tightly regulated

PS2-61

# Dysfunctional M2 Cortex-Superior Colliculus-Basal ganglia circuit in Huntington's disease

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Alterations in cortico-Basal ganglia (BG) circuitry are deeply characterized and profoundly compromised in Huntington's Disease (HD). However, little is known about the implications of subcortical-BG circuits in HD. The superior colliculus (SC) is a primitive subcortical sensorimotor area that integrates visual and cortical afferents (particularly from M2-Cortex (M2) and the cingulate) and modulates BG circuitry. Particularly, the cortico-SC-BG circuit is implicated in sensorimotor transformations to direct gaze movements, including the saccadic movements known to be altered in HD patients. Also, we recently described that activating M2 terminals in the striatum using optogenetics is sufficient to restore motor deficits in symptomatic HD mice. Here, we aim to identify and characterize structural and functional alterations of the M2-SC circuits in HD, to finally develop circuit based therapeutic strategies.

Our data shows that symptomatic HD mice (20 week) has predominant approach vs defensive behaviours compared to WT mice, seen by a significant reduction in active escaping response in the looming task and an increase in active approaches in the beetle mania task, indicating alterations in SC function in HD. Moreover, we used in vivo MRI to study functional connectivity from the M2 with BG-related structures at symptomatic stages. Our data demonstrates that the SC is one of the nuclei with higher functional correlation with the M2 in WT mice, and strikingly, significantly diminishes in symptomatic HD mice. Then, we injected AAV-CamKII-GFP in M2 and observed reduced axon terminals arriving to the SC in HD compared to WT mice. We are currently analyzing neuronal response to M2 activation in the SC by combining optogenetics with multielectrode arrays.

Our results describe for the first time the structural and functional involvement of the M2-SC-BG circuits in HD pathophysiology. By using optogenetics, we hope to modulate circuit function and restore symptoms in HD.

PS2-62

# Involvement of the neuropeptide cortistatin in neuroinflammation and blood-brain barrier dysfunction in ischemic stroke

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Ischemic strokes are the result of a permanent or transient occlusion of a major brain artery. The energy/oxygen deprivation that follows leads to irreversible tissue injury and long-term sequelae. Despite continuous improvements, therapeutic failure is still notorious and strokes remain the second cause of death worldwide. Therefore, many studies advocate that better stroke management requires focusing on endogenous neuroprotective mediators that globally modulate the immune response, rather than approaching pathogenic mechanisms independently. In this context, we study cortistatin (CST), a neuropeptide widely distributed in the Central Nervous System and the Immune System. This molecule displays anti-inflammatory, immunomodulatory and neuroprotective properties, characteristics that potentially make it an attractive endogenous target and a novel therapeutic agent for strokes. Hence, we are currently investigating its involvement in the immune dysregulation and neuroinflammation processes associated with strokes, as well as its possible therapeutic application. For this purpose, we use the MCAO (middle cerebral artery occlusion) model by temporarily (30') occluding the middle cerebral artery in WT and CST-deficient mice (CST-/-). Our preliminary results suggest more susceptibility to stroke development and worse prognosis in CST-/- mice 24h post-MCAO, i.e. larger neuronal lesions, higher neurological score and a striking acute glial activation. Moreover, blood-brain barrier (BBB) dysfunction in CST-/- mice may be also contributing to this great susceptibility, as shown in a BBB in vitro model, where the CST-/- endothelial cells barrier showed increased permeability and reduced and altered tight-junctions/adherens-junctions expression. Altogether, our results suggest the relevance of endogenous CST modulating neurodegeneration and neuroinflammation events during ischemic damage and its key role in the BBB structural and functional viability. Moreover, our findings add evidence supporting that recovering CST levels by its exogenous administration may be a novel multifunctional therapeutic agent for the treatment of ischemic strokes.

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PS2-63

# Transcriptomic analysis in a fragile X syndrome mouse model after CB1 receptor targeting reveals treatment-associated changes in RNA splicing machinery.

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Fragile X syndrome (FXS) is the most common monogenic cause of inherited intellectual disability and autism caused by the silencing of the FMR1 gene. The fragile X mental retardation 1 (Fmr1) knockout mouse shows cognitive impairment and some of the synaptic alterations observed in patients because of the loss of expression of the fragile X mental retardation protein (FMRP). Altough these alterations observed in the FXS mouse model have been restored by blocking the cannabinoid type-1 receptor (CB1R) with the systemic antagonist/inverse agonist rimonabant, the molecular hallmarks involved in these improvements are not yet fully understood. Since FMRP modulates local RNA translation at synapses to maintain synaptic activity and plasticity, we focused our analysis in a synaptoneurosome enriched fraction obtained from mice treated for seven days with rimonabant (0.1 mg/kg). We performed high-throughput RNA sequencing to analyse differential expression and splicing patterns between Fmr1 KO mice and WT after rimonabant or vehicle administration. Differential expression analysis at transcript level in Fmr1 KO synaptoneurosomes revealed the up-regulation of transcripts implicated in axon development and the down-regulation of transcripts related with synapse structure and organization, and mRNA processing. Notably, rimonabant treatment induced the upregulation of transcripts related with mRNA splicing. Furthermore, alternative splicing analysis of the same data showed a relevant number of transcripts producing different isoforms by exon skipping mechanisms in Fmr1 KO samples. Interestingly, these exon skipping events appeared to be regulated in opposite ways when Fmr1 KO mice were treated with rimonabant at low doses. Together, our transcriptomic analysis identifies a set of transcripts that may contribute to the aberrant synaptic phenotype in the FXS mouse model. Moreover, this analysis proposes that alternative splicing events described in Fmr1 KO mouse may be reverted after CB1 receptor inhibition under conditions that re-establish synaptic plasticity and memory perforamance.

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# PS2-64

## Increased serotonin 5-HT2A receptor constitutive activity on Gαi1-protein in post-mortem frontal cortex of subjects with schizophrenia

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In animal and cellular models, activation of Gαi1-proteins by serotonin 5-HT2A receptor (5-HT2AR) agonist drugs represents a molecular fingerprint of hallucinogenic properties. On the other hand, supersensitive 5-HT2AR signalling through Gαi1-, but not Gαq/11–proteins, has been observed in schizophrenia. If this supersensitivity is consequence of altered constitutive activity of 5-HT2ARs in schizophrenia, is still unknown. Currently, inverse agonists of 5-HT2ARs are available, which allows the analysis of constitutive activity conditions. In this context, pimavanserin has been described as selective 5-HT2AR inverse agonist on the Gαi1-protein-mediated pro-hallucinogenic pathway and neutral antagonist on the canonical Gαq/11-protein-mediated pathway, in human prefrontal cortex.
[35S]GTPγS binding assays associated to immunoprecipitation with specific antibodies for Gαi1- and Gαq/11-proteins were carried out with pimavanserin (10-10-10-6 M). The selectivity of pimavanserin on 5-HT2ARs was measured by using the antagonist MDL-11,939 (10 µM). Moreover, the selectivity was confirmed by using brain samples of wild-type (5-HT2AR(+/+)) and knock-out (5-HT2AR(-/-)) mice. Post-mortem frontal cortex samples from 23 subjects with schizophrenia and their matched controls were analysed.
Pimavanserin induced a higher inhibitory effect on 5-HT2AR coupling to Gαi1-proteins in schizophrenia subjects (Imax=20±2%) than in controls (Imax=14±1%) (p=0.0004). Pimavanserin did not induce effects on 5-HT2AR coupling to Gαq/11-proteins (Imax=0±1% and Imax=-1±1%, respectively). Pimavanserin activity on Gαi1-proteins was sensitive to MDL-11,939 confirming the involvement of 5-HT2ARs. Moreover, pimavanserin exerted a significant inhibition of the coupling to Gαi1-proteins (Imax=13±2%, n=6) in 5-HT2AR(+/+) mice, while no effect was found in 5-HT2AR(-/-) mice. No effect of pimavanserin on Gαq/11-proteins in mice brain tissue was observed.
These findings demonstrate an enhanced constitutive activity of 5-HT2ARs through the pro-hallucinogenic pathway in prefrontal cortex of subjects with schizophrenia. The constitutive 5-HT2AR hyperactivity could underlay the vulnerability to psychotic symptoms and suggest the relevance of the inverse agonism on 5-HT2ARs as new anti-psychotic pharmacological strategy.

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PS2-65

# Functional selectivity of serotonin 5-HT2A receptor drugs on Gαi1-proteins in postmortem human brain cortex

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Cell culture and animal studies have demonstrated that both hallucinogenic and non-hallucinogenic 5-HT2A receptor (5-HT2AR) agonists promote Gαq/11-protein activation. In contrast, only hallucinogenic drugs acting at 5-HT2ARs activate inhibitory Gαi1-proteins. Whether these mechanisms operate in brain tissue remains unknown.

The activation of 5-HT2AR coupling to Gαi1- and Gαq/11-proteins induced by hallucinogenic ((±)DOI and LSD) and non-hallucinogenic (lisuride and pergolide) 5-HT2AR drugs was evaluated at 10 µM concentration in post-mortem human brain cortex. The effects of different 5-HT2AR antagonist/inverse agonists (pimavanserin, altanserin, nelotanserin, eplivanserin, volinanserin and ketanserin) on both pathways were also analysed. Modulation of the [35S]GTPγS binding coupled to antibody immunoprecipitation by using the Scincillation Proximity Assay (SPA) technology was chosen as methodological approach.

(±)DOI and LSD increased the [35S]GTPγS binding to both Gαi1- and Gαq/11-proteins by a mechanism sensitive to selective 5-HT2AR antagonists (MDL-11,939, ketanserin and altanserin). Other inhibitory Gαi/o-protein were also stimulated but less sensitive to 5-HT2AR antagonists. Moreover, equivalent stimulatory effects on both pathways were observed in brain of wild-type mice and disappeared in 5-HT2AR knock-out animals. The non-hallucinogenic drugs lisuride and pergolide behaved as 5-HT2AR agonists exclusively on the Gαq/11-protein pathway. On the other hand, pimavanserin, altanserin, and volinanserin exerted an inhibitory response on the [35S]GTPγS basal binding to Gαi1-proteins that was sensitive to MDL-11,939 and absent in 5-HT2AR knock-out mice, confirming their inverse agonist properties on this 5-HT2ARs pathway. Regarding 5-HT2AR coupling to Gαq/11-proteins, only volinaserin displayed inverse agonism.

These results demonstrate a differential profile of G-protein signalling between hallucinogenic and non-hallucinogenic 5-HT2AR agonists in human brain cortex. The functional coupling to Gαi1-proteins may be involved in the hallucinogenic liability of (±)DOI, LSD and other 5-HT2AR agonists. These results also suggest that selective inverse agonism contributing to uncoupling of 5-HT2ARs from Gαi1-proteins could be a new pharmacological approach in the development of new antipsychotic drugs.

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PS2-66

# BCAS1 defines a heterogeneous population in oligodendroglioma and glioblastoma

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Glial-derived tumors such as oligodendrogliomas (OGs) and glioblastomas (GBs) account for the majority of CNS tumors. OG is a type of diffuse glioma, characterized by IDH1/2 mutations and 1p/19q co-deletion. OGs are subclassified into grade II and III according to malignancy. GBs, on the other hand, are the most aggressive type of glioma (grade IV). The cell of origin of these neoplastic entities is still elusive. However, different state-of-the-art studies point towards immature oligodendrocytes as a possible source of gliomagenesis. Therefore, studying markers that identify oligodendrocyte precursors has become of great interest. Breast carcinoma amplified sequence 1 (BCAS1) has emerged as a novel marker that defines an immature oligodendrocyte population. This marker has been associated to non-CNS tumors. In this study we analyzed the expression of BCAS1 in a series of surgically removed OGs (n=17) and GBs (n=58). To study the distribution and proliferative status of the different cell subpopulations within OG and GB, we co-stained BCAS1, with EGFR, Vimentin and Ki-67. Additionally, we analyzed the ultrastructure of BCAS1+ cells by immunoelectron microscopy. We performed stereological quantification of the cell density and proliferation of BCAS1+ cells and compared them to EGFR+ proliferative cells. Our results depict that BCAS1+ cells constitute a heterogeneously distributed population in glial-derived tumors. This population displays two different morphologies: stellate or spherical cells. In particular, stellate cells can form tightly packaged nodules and present a high proliferative rate when compared to EGFR+ cells. Statistical analysis show that BCAS1+/Ki67+ cells increase according to the malignancy of the tumor. Nevertheless, the density of BCAS1+ cells decreases in more aggressive tumors. This suggests that BCAS1 is a marker defining a specific cell subpopulation within diffuse gliomas, which could correspond to a state of transient amplification, thus contributing to tumor malignancy.

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PS2-67

# Antidepressant actions of ketamine engage cellular mechanisms of endoplasmic reticulum stress by the eIF2α pathway

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Chaperone proteins and folding enzymes in endoplasmic reticulum (ER) perform a key role in proteostasis, which can be disrupted by numerous factors leading to an accumulation of unfolded proteins in the lumen. It results in ER stress and unfolded protein response (UPR) is elicited to restore homeostasis. However, under prolonged cellular stress, the UPR pathway can lead to cell dysfunction/loss. Impaired ER mechanisms are responsible for neurodegeneration in numerous human diseases and there is also growing evidence that ER stress is implicated in the neuronal dysfunctions of neuropsychiatric disorders. The present study was aimed to check the hypothesis that ER stress and UPR pathway over-activation in the serotonin (5-HT) neurons are involved in the cellular pathological mechanisms of anxiety and depression by causing an impaired proteasome function. ER stress was induced by a single local application of tunicamycin (200 µg/µl) in dorsal raphe nucleus of mice. We examined tunicamycin effects on proteins related to ER stress, UPR, and apoptosis, on serotonin function as well as on anxiety- and depression-like behaviors. Tunicamycin rapidly induced ER stress in 5-HT neurons, leading to a time-dependent increase in GRP78 protein levels. Furthermore, CHOP protein, which triggers apoptosis pathways, was also increased 7 days after tunicamycin infusion. ER stress led to an increased eIF2α and eEF2 phosphorylation, suggesting the activation of PERK pathway in 5-HT neurons. Tunicamycin-treated mice exhibited an anxious-depressive phenotype and showed altered 5-HT neurotransmission in medial prefrontal cortex. A single dose of ketamine (10 mg/kg, ip) reversed the depressive phenotype 30 minutes post-administration, which is linked to reduced levels of phosphorylated eIF2α and recovery of proteostasis. The results strongly indicate that ER stress and UPR may represent cellular pathogenic mechanisms in the development of mood disorders and the eIF2α pathway is central for antidepressant activity of ketamine.

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PS2-68

# A closer look at Cux1 heterozygosis in the neocortex, when one copy is not enough

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Neurodevelopmental disorders can emerge due to abnormal neuronal function and/or connectivity. Cortical wiring requires a variety of neuronal subtypes which identity is defined by specific transcription factors (TF). Some of them are dosage-dependent, meaning that a single functional copy of the gene cannot maintain the phenotype. In the neocortex, upper layer neurons, which participate in the most complex and evolved circuits, are defined by the expression of Cux1 TF. This gene is involved in their dendritogenesis, synaptogenesis, and the establishment of interhemispheric projections as shown by knock-down experiments. Moreover, heterozygous patients carrying a mutant Cux1 allele have neurological diseases such as epilepsy, intellectual disability, and autism spectrum disorder. However, the overall cortical development and brain structures seem normal in heterozygous condition. Thus, a deeper characterization of the heterozygous scenario is needed. For this purpose, we have studied Cux1 expression in different functional areas of the cortex during development by immunostaining; performed a battery of neonatal motor tests in Cux1 heterozygous mice; analysed their susceptibility to kainate-induced seizures, and investigated a possible axonal dysfunction in these neurons. Our results show a significant reduction of Cux1 expression in the neocortex at postnatal day (P) 10, specially in the barrel field of the somatosensory area. These differences are attenuated in adulthood (P30), suggesting a possible rescue mechanism that leads to a catch-up phenotype. We also demonstrate that Cux1 heterozygosis increases predisposition to develop seizures in mice. Taking together, our findings highlight the relevance of Cux1 levels of expression during cortical development and point to the necessity of investigating the consequences of Cux1 haploinsufficiency at a molecular level.

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PS2-69

# Immunodensity of dopamine D2, cannabinoid CB1, metabotropic glutamate mGlu2 and mGlu3 receptors in schizophrenia subjects

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Background: Dysregulation of dopamine D2 (D2R), cannabinoid CB1 (CB1R) and/or metabotropic glutamate 2/3 (mGlu2/3R) receptors may contribute to the pathophysiology of schizophrenia. The aim of this study was to quantify the immunodensities of D2R, CB1R, mGlu2R and mGlu3R in post-mortem brains of schizophrenia subjects.

Material and methods: Brain samples from the dorsolateral prefrontal cortex (DLPFC; Brodmann's area 9) of subjects with schizophrenia (n=48) and sex-, age-, and post-mortem interval-(PMI) matched controls (n=48) were obtained at autopsies performed in the Basque Institute of Legal Medicine. Schizophrenia cases were divided into antipsychotic-treated (AP+; n=29) and antipsychotic-free (AP–; n=19) groups, according to blood toxicological screening at death. Receptor cortical amounts were estimated by Western blot (WB). Antibody selectivity was validated in knockout mice lacking target receptors. Case-control datasets were compared by paired t-tests.

Results: The immunodensities of both mGlu2R (–31%; $p<0.001$) and CB1R (–17%; $p<0.01$) were significantly lower in schizophrenia, compared to those in control brains. Regarding the antipsychotic treatment, CB1R downregulation was only observed in AP+ cases (–18%; $p<0.05$), whereas mGlu2R expression was reduced both in AP– cases (–27%; $p<0.05$) and more robustly in AP+ subjects (–34%; $p<0.001$). In contrast, D2R and mGlu3R cortical amounts did not differ significantly between cases and controls.

Conclusions: The present results indicate that low mGlu2R protein expression might be a core feature of the schizophrenia brain, which could be further aggravated following antipsychotic treatment. On the other hand, downregulated CB1R levels might be attributed to antipsychotic medication. Surprisingly, D2R and mGlu3R protein expression did not seem to be altered in the DLPFC of schizophrenia subjects. However, this does not imply that the functional signalling of these receptors is not altered. Future studies will determine the implications of mGlu2R dysregulations in schizophrenia brain functioning.

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PS2-70

# Generation and characterisation of new mouse models of TDP-43 proteinopathies including a new genomically humanised Knock-In strain

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TDP-43 (encoded by the TARDBP gene) is the main component of the pathogenic inclusions that define the great majority of cases of amyotrophic lateral sclerosis (ALS) and ~50% of frontotemporal dementia (FTD) cases. Moreover, mutations in TARDBP are causative of ALS and/or FTD. Despite its critical role in these neurodegenerative diseases, it is not yet clear how TDP-43 dysfunction leads to neurodegeneration.

To try to recapitulate as faithfully as possible human ALS disease pathogenesis, we have a long-term interest in creating Knock-in (KI) mouse models of ALS. Here, we present the characterization of a novel TDP43 mutant Knock-in mouse line carrying a pathogenic point mutation within the C-terminal domain of TDP43 (Q331K). We include behavioral analysis of this strain on a B6 and B6/DBA background as well as cellular and molecular analysis of derived primary cell lines. As other C-terminal mutations, the Q331K mutation leads to a splicing gain of function, as well as stress response abnormalities and dysfunction in pathways previously associated with ALS pathogenesis, such as the PI3K pathway.

In addition, we present the generation and initial molecular characterisation of the first genomically humanized TDP-43 (hTARDBP) mouse model, on which we have replaced the mouse Tardbp gene for its human TARDBP counterpart, from the start to the stop codon, including all introns in between, producing the first mouse model expressing a human TDP-43 protein under mouse endogenous physiological expression control.

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PS2-71

# A new non-aggregative splicing isoform of human Tau is decreased in Alzheimer's disease.

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Tauopathies, including Alzheimer's disease (AD) and frontotemporal lobar degeneration with Tau pathology (FTLD-tau), are a group of neurodegenerative disorders characterised by Tau hyperphosphorylation. Post-translational modifications of Tau such as phosphorylation and truncation have been demonstrated to be an essential step in the molecular pathogenesis of these tauopathies. In this work, we demonstrate the existence of a new, human-specific truncated form of Tau generated by intron 12 retention in human neuroblastoma cells and, to a higher extent, in human RNA brain samples, using qPCR and further confirming the results on a larger database of human RNA-seq samples.

Furthermore, diminished protein levels of this new Tau isoform are found by Westernblotting in Alzheimer's patients' brains with respect to non-demented control subjects, suggesting that the lack of this truncated isoform may play an important role in the pathology. This new Tau isoform exhibits similar post-transcriptional modifications by phosphorylation and affinity for microtubule binding, but more interestingly, is less prone to aggregate than other Tau isoforms. Finally, we present evidence suggesting this new Tau isoform could be linked to the inhibition of GSK3β, which would mediate intron 12 retention by modulating the serine/arginine rich splicing factor 2 (SRSF2).

Our results show the existence of a potentially relevant new isoform of Tau and suggest that further research on this less aggregation-prone Tau may help to develop future therapies for Alzheimer's disease and other tauopathies.

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PS2-72

# Synergistic effects of applying Static Magnetic Fields and Diazepam to Control EEG Abnormalities in an Epileptic Rat Model

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In previous work, we have found that transcranial static magnetic fields (tSMS) application was able of delaying and reducing EEG seizure signs in the lithium-pilocarpine rat model of epilepsy1. Here we explore the putative synergistic effect of combining tSMS with low doses of diazepam, a drug commonly used to treat status epilepticus.

Experiments were carried out on 8 Sprague-Dawley rats, 2-3 months old. LiCl (127 mg/kg, i.p.) was administered 24 hours before pilocarpine injections. Pilocarpine was given in two doses injected (i.p.) 30 min apart. The first one was preceded (30 minutes) by Scopolamine, 1 mg/kg. Animals were randomly classified into two groups: “Magnet” (a neodymium nickel-plated cylinder, 45mm diameter and 30mm height, magnetic field of 0.5T was placed over the skull just before the first pilocarpine injection and for a total period of one hour), or “Control” (a stainless steel replica without magnetic properties was used). 1.25 mg/kg of diazepam (i.p.) was injected sixty minutes after of the second dose of pilocarpine.

Thirty minutes after diazepam injection, there was a clear reduction in the number of EEG spikes in both groups, being more pronounced in the magnet group (T-test, $p<0.05$). The Root Mean Square -an estimation of the EEG amplitude- showed a greater reduction in the Magnet group compared with those animals that only received the diazepam dose (T-test, $p < 0,001$). Furthermore, the power spectrum analysis showed a stronger reduction in theta, alpha and beta bands, on the diazepam+magnet animals compared to the diazepam+sham group (T-test, $p < 0.05$ beta band; T-test, $p< 0.0001$ theta and alfa bands).

The results show synergistic actions between magnetic fields and diazepam in controlling EEG abnormalities in the epilepsy model used here, and pave the way for the combination of tSMS with pharmacological treatments for epilepsy, improving seizures control and, perhaps, allowing dose reduction.

PS2-73

# Mitochondrial dysfunction and neurotoxicity induced by frataxin deficiency in astrocytes are attenuated with the Sonic Hedgehog agonist SAG

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Friedreich´s ataxia (FRDA) is predominantly a neurodegenerative disease caused by a deficiency in frataxin (FXN). FXN is a protein with a major mitochondrial localization enriched in tissues with a high-energy demand, like the brain. These low FXN levels lead to a progressive degeneration of neurons of the spinal cord, brainstem and the deep cerebellar nuclei, responsible for the loss of movement coordination and equilibrium, main symptoms observed in FRDA patients.

As for other neurodegenerative diseases, increasing evidence supports the idea that other non-neuronal cells like astrocytes are actively involved in the FRDA neurodegenerative process. Depending on the stimuli they respond to, astrocytes acquire different activation states in a process called astrogliosis, where neuroinflammatory stimuli induce the formation of A1 reactive astrocytes, which upregulate proinflammatory genes, being harmful for neurons. Recent studies have demonstrated positive effects of Sonic Hedgehog (SHH) agonists in astrocyte viability and proliferation, astrocyte-mediated neuroprotection, and also positive effects in mitochondrial activity and dynamics. Thus, we have thoroughly characterized astrocyte reactivity phenotype and mitochondrial status of FXN-deficient astrocytes, evaluating as well the effect of SHH agonists on astrocyte reactivity, viability, and function.

We have observed that FXN-deficient astrocytes have reduced cell viability and higher expression of several A1 reactive astrocyte markers. Moreover, FXN-deficient astrocytes also showed defects in mitochondrial function and dynamics. All these alterations were prevented by a chronic treatment with the smoothened agonist (SAG), a SHH signaling agonist. Regarding the possible neuroprotective effects of SHH agonists, previous results showed that FXN-deficient astrocytes are able to induce neurodegeneration, and we have observed that the chronic treatment with SAG attenuated the neurotoxicity triggered by the treatment of mouse cortical neurons with conditioned medium of FXN-deficient astrocytes.

Overall, our results indicate that astrocytes might be considered as key players in the neurodegenerative process associated with FRDA, suggesting as well that the treatment of FXN-deficient astrocytes with a SHH agonist like SAG, could be used as a possible target to reduce FRDA-associated neurodegeneration.

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PS2-74

# Sperm cytoskeleton ODFs genes as a potential mechanism of glioblastoma progression

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Glioblastoma (GB) is the most common and aggressive malignant primary brain tumor of the central nervous system in humans, it is originated from neoplastic glial cells. GB affects 1/100.000 persons and the median survival is 14,6 months. Neoplastic glial cells are characterized by a high degree of proliferation, diffuse invasion and resistance to conventional therapies. Patients suffer from synapse loss, an early symptom of a neurodegenerative processes. Our group has demonstrated that Drosophila GB cells extend a network of tumor microtubes (TMs) that enwrap the surrounding neurons, and promote glia–neuron signaling communication that favors glial proliferation and invasion, leading to a reduction of synapse number in the neighboring neurons. All these results suggests that GB is a neurodegenerative disease.

We use Drosophila melanogaster as a model of GB based on the constitutive activation of PI3K and EGFR in glial cells, this GB model faithfully reproduces the progression of the tumor, and associated-neurodegeneration. Our group is focused in GB growth mechanisms through TMs and I study the role of ODFs as potential network modulators. I study the role of dODF3B and dODF3L2, that have human orthologues upregulated in glioma, and correlate with poor prognosis.

We have found that dODFs act as sperm actin cytoskeleton modulators and are upregulated in GB brains, correlating with tumor progression. More specifically, the downregulation of dODF3B and dODF3L2 in GB cells prevents GB proliferation, infiltration and neurodegeneration. In addition, preliminary results suggest that signaling pathways described in GB as WNT/Wg modulate dODF3B levels of expression in glial cells. Consequently, we suggest that dODFs emerge as potential targets involved in glia-neuron communication, and GB progression.

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PS2-75

# Auditory evoked oscillations are altered in UBE3A knock-out rat model of Angelman's syndrome

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Angelman's syndrome (AS) is a severe neurodevelopmental disease caused by a lack of function of a segment of chromosome 15. Most of the time it is related to a deletion or mutation of the UBE3A gene on that chromosome. The electroencephalogram (EEG) in AS is usually abnormal and may be used as a quantitative biomarker for differential diagnosis, to track progression, and as clinical outcome estimate.

Here we investigate the effect of UBE3A deletion on the spontaneous activity and auditory-evoked responses by using a UBE3A knock-out rat model of AS. To do that, we explored the ongoing activity (qEEG), the auditory steady state responses (ASSR, oscillatory responses to rhythmic auditory stimuli) and the chirp-EP responses (responses related to a tone modulated in amplitude at increasing frequencies) under open-field, freely-moving conditions.

Spectral analyses suggest a decrease in gamma oscillatory activity at the frontal cortex in knock-out rats when compared to wild-type. Interestingly, robust changes in the ASSR and chirp-EP were found. The 40-Hz ASSR evoked activity and intertrial coherence were increased for transgenic animals. Similarly, the chirp-EP evoked activity and intertrial coherence were increased in a region at around 60 Hz. These differences are found bilaterally in the frontal cortex but not in the parietal cortex, suggesting a region specific disruption of neuronal synchronization mechanisms in the UBE3A knock-out rats. If replicated in patients, the ASSR and chirp-EP could constitute a useful biomarker for AS, guiding pharmacological development of therapies that target aberrant neuronal function.

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PS2-76

# Expression of microglial CX3CR1 in Alzheimer's disease and its regulation by noradrenaline

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Noradrenaline (NA) is a major modulatory neurotransmitter of the central nervous system (CNS) and besides its actions as a neurotransmitter it presents a potent anti-inflammatory and neuroprotective effect. The major source of NA in the CNS is the Locus coeruleus (LC) which is one of the earliest brain region affected by Alzheimer's disease (AD). The loss of noradrenergic neurons in LC leads to a decrease in NA levels which facilitates the progression of AD. This seems to be due mainly to the ability of NA to reduce the activation of microglial cells. We previously observed that NA induces the production of the chemokine CX3CL1 in neurons. The activation of microglial CX3CR1, receptor for CX3CL1, reduces the activation of microglia, which is known to contribute to the neuronal damage characteristic of AD. Therefore, alterations of CX3CR1 production in microglia could translate into an alteration of CX3CL1 anti-inflammatory effects.

In order to determine if microglial CX3CR1 production is altered in AD and if NA can regulate it, CX3CR1 expression and synthesis were analyzed in 5xFAD mice and human AD brain samples. In addition, the effects of NA and its reuptake inhibitor reboxetine were analyzed in microglial cultures and 5xFAD mice respectively.

Our results indicate that the production of CX3CR1 is increased in the brain cortex of AD patients and 5xFAD mice. Also, in these mice reboxetine treatment further increases CX3CR1 and enhances microglial reactivity toward amyloid beta plaques. However, administration of NA to cells cultures of primary rat microglia or HMC3 cell line decrease CX3CR1 production, suggesting that microglia responses to NA may be altered in the absence of CX3CL1-producing neurons or other external factors.

PS2-77

# Assessment of the integrity of the endothelial junctions and blood-brain barrier disruption in MCT8 deficiency

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Thyroid hormones (TH) are essential for the proper development of the brain. TH need transmembrane transporters to access their specific tissues and target cells. The monocarboxylate transporter 8 (MCT8) exclusively transports TH and is crucial for the maintenance of adequate contents of TH in the brain.

Allan-Herndon-Dudley Syndrome (AHDS) or MCT8 deficiency is a rare X-linked disease due to inactivating mutations in the SLC16A2 gene, which encodes for the MCT8 transporter. AHDS is characterized by peripheral hyperthyroidism and by cerebral hypothyroidism due to impaired transport of TH across the blood-brain barrier (BBB). Patients with AHDS present symptoms such as delayed neurological development and severe psychomotor disorders.

The aim was to assess the integrity of the BBB by analyzing the ultrastructure of the neurovascular unit in an animal model of MCT8-deficiency: the Mct8/Dio2 KO mouse. We used transmission electron microscopy) to evaluate the organization of the tight junctions and the pericyte and astrocyte end-feet coverage of the blood vessels. We also analyzed the expression of tight junction proteins by western blot, to confirm the ultrastructural defects of the neurovascular unit observed by electron microscopy. The functionality of the BBB was also assessed by the quantification of the infiltration of sodium fluorescein dye in the Mct8/Dio2 KO brain compared to controls. Finally, the blood-vessel density of the whole brain was studied by angiography neuroimaging.

Our results could provide new therapeutic targets and biomarkers associated to the neurological symptoms of the AHDS and can contribute to the generation of new therapeutic strategies to improve the quality of life of MCT8-deficient patients.

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PS2-78

# The role of extracellular vesicles in Alzheimer's disease: mechanistic insight into intrinsic protection

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Alzheimer's disease (AD) is the leading cause of dementia worldwide (>30 million people affected). The cause of the disease is unknown, and there is no causal treatment. The gradual deterioration of cognitive functions in AD is paralleled by a hierarchical progression of amyloid-plaques (Aβ) and hyperphosphorylated Tau protein in the brain, which suggests that propagation of these aggregates has a role in the pathophysiology of the disease. Extracellular vesicles (EVs), including exosomes and microvesicles, are membranous nano/micro-structures released by most, if not all, cells. EVs carry proteins, lipids, and nucleic acids (DNA, mRNA, and miRNA), and they participate in cell-to-cell communication. However, the functionality and regulation of EVs (secretion, uptake, and cargo delivery) are not fully understood in the brain, where EVs have been related to essential functions such as neurotransmission and myelin maintenance. Recently, EVs emerged as relevant factors in neurodegenerative diseases, especially in AD, and they were described as disease biomarkers in the patient's fluids. Interestingly, they seem to have a dual role in AD: spreading pathological aggregates (Aβ and p-Tau) on the one hand and neuroprotection against the progression of the pathology on the other hand.

Here we will describe the biology of EVs in AD in detail. We will characterize the composition and cellular source of EVs and their uptake mechanisms throughout AD progression. EVs from the brains of AD patients and age/sex-matched controls will be obtained, and their RNA and protein profiles will be characterized by novel transcriptomic and proteomic work-ups. Moreover, hiPSCs-derived neuronal cultures will be used as a model to elucidate the role of these AD-derived EVs.

Our main goal is to generate mechanistic insight into EVs' neuroprotection in AD by combining deep phenotyping of patient-derived EVs with hypothesis-driven experiments in hiPSC to open the door to new EV-based AD treatment options.

PS2-79

# Δ9-TETRAHYDROCANNABINOL PROMOTES FUNCTIONAL REMYELINATION IN THE MOUSE BRAIN

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Δ[9]-Tetrahydrocannabinol (THC), the most prominent active constituent of the hemp plant Cannabis sativa, confers neuroprotection in animal models of multiple sclerosis (MS). However, the possible effect of THC on oligodendrocyte regeneration and myelin repair has never been studied. Here, by using oligodendroglia-specific reporter mouse lines in combination with 2 models of toxin-induced demyelination, we show that THC administration enhanced oligodendrocyte regeneration, white matter remyelination, and motor function recovery. Interestingly, THC also promoted axonal remyelination in organotypic cerebellar cultures ex vivo. THC remyelinating action relied on the induction of oligodendrocyte precursor cell cycle exit and differentiation via CB1 cannabinoid receptor activation. Overall, our study identifies THC administration as a promising pharmacological strategy aimed to promote functional CNS remyelination in demyelinating disorders as MS.

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PS2-80

# Astrocytic GLUT1 ablation improves systemic glucose metabolism and promotes cognition

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Glucose supply from the blood to the brain is controlled by the glucose transporter GLUT1, highly expressed in astrocytes, which coordinate brain glucose supply, metabolization and storage. Ablating GLUT1 at the blood-brain barrier (BBB) endothelial cells leads to BBB breakdown, brain glucose hypometabolism and impaired cognition, but this approach cannot discriminate between insufficient glucose supply and BBB breakdown-derived effects. Such question is the focus of the present work, which aims to elucidate the relevance of astrocytic GLUT1 to cellular, brain and systemic glucose metabolism, and to cognition.

To address these questions, GLUT1 was ablated from primary astrocytes. Real-time cellular metabolism was examined using an extracellular flux analyzer (Seahorse) and gene expression studies. In vivo, astrocytic GLUT1 was ablated using a tamoxifen-inducible Cre/LoxP approach (GLUT1ΔGFAP mice). 18F-FDG PET, glucose and insulin tolerance, insulin secretion and fasting-induced hyperphagia were characterized. Cold exposure, histology and gene expression were used to study brown adipose tissue (BAT) activity. BBB integrity was examined by vessel immunostaining and capillary-depleted brain analysis. Recognition and spatial memory were assessed using Novel Object Recognition and Morris Water Maze tasks.

GLUT1-ablated astrocytes showed reduced glucose uptake and glycolysis, although preserving total ATP production. Unexpectedly, postnatal astrocytic GLUT1 deletion increased CNS glucose utilization. GLUT1ΔGFAP mice showed an improved metabolic status from which obese animals especially benefited. Specifically, GLUT1ΔGFAP mice were more efficient at suppressing hyperphagia and readjusting systemic glucose levels after hyperglycemia, exhibiting markedly increased insulin secretion. These effects were coupled with enhanced BAT activity, and reduced BAT adiposity. In parallel with this improved systemic homeostasis, GLUT1ΔGFAP mice performed both recognition and spatial memory tasks properly, even outperforming control mice.

Overall, this study demonstrates that astrocytic GLUT1 ablation impairs astrocytic glucose availability but enhances brain glucose utilization, reprograms systemic glucose metabolism towards a more efficient glucose-handling phenotype and promotes cognitive abilities.

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PS2-81

# Hypothalamic anorexigenic and orexigenic gene expression after morning or evening forced wheel exercise in adolescent rats

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Physical activity became an effective way to modify the body composition. Changes in body composition during adolescence can affect manifestation of diseases such as obesity or diabetes later in life. In a previous work we found that males showed decreased adipose tissue contents after an exercise program with morning and evening sessions (2 sessions a day). Here, were analyzed the training effects during either morning or evening sessions in body composition and their molecular hypothalamic changes.

In this study P20 adolescent rats (n=24) were trained in a forced program until P60. Different groups trained at ZT13 (n=6 AM exercise, n=6 AM sedentary) or at ZT23 (n=6 PM exercise, n=6 PM sedentary). On P24 and P57, the whole body of the rats was analyzed through computerized tomography. Food and water intake were measured every 24 hours. On P60, the hypothalamic region was removed, snap-frozen in under 10 minutes after sacrifice, and stored at -80C until the mRNA isolation, cDNA synthesis and qPCR study. All the procedures regarding the qPCR methodology were performed by following the MIQE guidelines. Statistical analysis and graphs were performed with GraphPad Prism 9.

Only the PM exercise group showed lower adipose tissue content ($p<0.05$). Both exercise groups showed higher lean content than the respective control groups ($p<0.05$). No differences were observed regarding body weight or body volume between the groups ($p>0.05$). No differences were observed in the food intake or the orexigenic/anorexigenic genes expression Pomc, Agrp, Npy, Cartpt ($p>0.05$).

Our results suggest that the effects of morning or evening exercise on the body composition are not related to intake differences. Further studies are required to elucidate the molecular mechanisms responsible of these differential effects of exercise, dependent on the time of the day.

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PS2-82

# IGF1 modulates inflammation and phagocytosis in reactive astrocytes through PI3K(p110α) in a sex-specific manner.

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During the last years, increasing evidence suggests that male and female brains react differently to insults. However, little is known about the mechanisms underlying this differences. Insulin-like growth factor-1 (IGF1) is a neuroprotective factor involved in regulating processes such us neurogenesis, synapse formation, anti-inflammation and phagocytosis in brain damage situations.

To investigate the role of IGF-1 in regulating neuroinflammation, we use a systemic treatment with Lipopolysaccharide (LPS) that induced an increase of GFAP expression, which was abrogated by IGF-1 treatment only in males. In primary astrocyte cultures treated with LPS and IGF-1, we measured the levels of pro-inflammatory molecules by q-RTPCR and astrocyte engulfment of CY3-conjugated neuronal debris. LPS induced an increase of mRNA levels of TLR-2 and 4, iNOS, IP-10, IL-1β, IL-6 and IL-10 in both sexes and a decrease of IRAK4 mRNA expression specifically in male astrocytes. The treatment with IGF1 was able to counteract the effect of LPS on mRNA expression of TLR4 in both sexes and the expression of IRAK4, iNOS, IL-6 and IL-10 mRNA only in males. Furthermore, also in male astrocytes stimulated with LPS, IGF-1 induced an increase in neural debris phagocytosis.

To evaluate the involvement of PI3K/AKT pathway in IGF-1 regulation, specific inhibitors of PI3K catalytic subunits p110α, p110β and p110δ, were tested. Only p110α inhibitor counteracted the effects of IGF-1 in male astrocytes, with no significant effects on females. Although all the catalytic subunits interact physically with IGF1-R in both sexes, the level of expression of p110α is higher in male reactive astrocytes treated with IGF-1 than in females.

Taken together, our results reveal that IGF-1 affects the inflammatory and phagocytic function of astrocytes through a specific and sexually dimorphic interaction between IGF-1R and p110α.

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PS2-83

# A novel modular toolbox for precise neuronal epigenome editing

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Targeted editing of the neuronal epigenome has become a key methodology to improve our understanding of epigenetic function and regulation. These methods may also lead to the development of novel therapies to treat epigenome-associated diseases. Among epigenome editing systems, the use of CRISPR (Clustered Regularly InterSpaced Palindromic Repeats) stands out for its versatility, ease of engineering, and cost-effectiveness. The chimeric fusion of the nuclease-deficient dCas9 with epigenetic enzymatic activities enables locus-specific rewriting of epigenetic information by guide RNAs. However, the resulting chimeric proteins are often large in size and beyond the packaging capacity of the viral vectors most commonly used in neuroscience. To overcome this limitation, we have developed a novel, modular toolbox in which chimeric proteins are split into two smaller constructs taking advantage of nanobodies' ability to bind with high affinity to the recognized epitope. More precisely, the dCas9 protein was fused to a nanobody that specifically recognizes GFP and GFP was fused with the catalytic domain of different effector proteins. We targeted our tool to unique promoters of the gene encoding the brain-derived neurotrophic factor, Bdnf, which due to its complex transcriptional regulation and pivotal role in synaptic plasticity and memory is a particularly relevant candidate for epi-editing. Results combining our tool with synthetic and epigenetic effector modules highlight the potential of this novel toolbox for precise neuronal epigenome editing and open new opportunities to elucidate the role of epigenetic mechanisms in the regulation of gene expression in both physiological and pathological conditions.

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PS2-84

# USE OF BIORESORBABLE NANOPATTERNED POLYMER SCAFFOLDS AS A STRATEGY TO GUIDE THE MIGRATION OF NEURAL AND DENTAL STEM AND PROGENITOR CELLS.

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Injuries in the central nervous system (CNS) and nerve lesions have a strong impact on high financial expenses and quality of life for the patients. We present a nanostructured polymer scaffold based on bioresorbable elastomeric co-polyesters functionalized with graphene derivatives to promote the attachment, alignment and migration of stem and progenitor cells of neural (murine origin, mNSC, control) or dental pulp stem cells (human origin, hDPSCs). hDPSCs present substantial advantages with respect to other types of stem cells for CNS therapy, as hDPSCs express neural markers and neurotransmitter receptors and have an excellent capability to be differentiated towards neural lineage due to its neural crest origin. hDPSCs are resistant to hypoxic conditions & highly accessible, secrete neurotrophins and anti-inflammatory factors.

Scaffolds of lactide and caprolactone based copolyesters were first nanopatterned with gratings of 300 nm linewidth and subsequently functionalized with polydopamine, which acted as an adlayer for the final immobilization of graphene oxide (GO). mNSCs or hDPSCs were seeded and videorecorded on these scaffolds for 72h. After 3, 7 and 10 days, cells were fixed and immunostained for neuronal and glial markers. Furthermore, the interactions, cell-to-cell contacts and synaptic connections were analyzed by SEM.

Both type of stem cells instead of grow forming neuro / dentospheres, sedimented attached and elongated following the nanograting axis generating chains of cellular migration. Immunohistochemistry analyses showed the persistence of both neuronal and glial markers when seeded on GO-functionalized nanostructured scaffolds compared with the control. Furthermore the scaffolds were compatible with intracranial transplantation allowing to connect brain with olfatory bulb in a partially bulbectomized murine model.

The combination of a nanostructured bioresorbable polymeric scaffold together with the functionalization of the surface with GO enables a simple and scalable method to align and guide the migration of neural and progenitor stem cells for future neuroregenerative therapies.

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PS2-85

# Generation of an in vitro assay to evaluate antipsychotic drug effects on synaptogenesis

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Atypical antipsychotics (AAPs) drugs, such as clozapine, remain the current standard treatment for schizophrenia in clinical practice. Although they directly recognize the orthosteric binding site of G-protein coupled receptors, these drugs have a very high affinity for the serotonin 5-HT2A receptors expressed in the central nervous system. Preliminary results from our group suggest an intrinsic activity of clozapine when interacting with 5-HT2A receptors aside from the activation of signaling effectors depending on G-protein coupling. We have also found that chronic clozapine treatment negatively regulates synaptic remodeling and cognition in experimental animals. However, further investigations are needed for understanding the molecular mechanism of action of AAPs.

In order to study the effects of AAPs in synaptogenesis beyond the classical heterologous expression systems, we have generated an in vitro model based on the culture of neural stem (NS) cells obtained from murine fetal forebrain tissue for the subsequent differentiation into cortical neurons. Fetal frontal cortex is obtained at embryonic day 12 (E12) and the resulting cellular suspension is cultured using a specific culture medium. These NS cells grow as adherent monolayer cultures which can be easily differentiated into neurons using selective culture mediums. Neurons derived from fetal NS cells represent an ideal in vitro model mirroring the physiological system where AAPs perform their action through 5-HT2A receptors.

Using this in vitro model, we have established an assay based on the rabies virus technology, which constitutes an unique monosynaptic tracer to unambiguously label directly connected neurons, in order to explore the AAPs effects on neuronal synaptogenesis and neuronal plasticity. Using the selective and retrograde spread of the rabies virus we are able to identify the initial rabies-infected cells and the presynaptically connected neurons, constituting an ideal approach to study synaptogenesis and mechanism of action of APPs.

PS2-86

# Virtual Water Maze For Human Memory Assessment Synchronized With Transcranial Magnetic Stimulation

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The Morris Water Maze task has been used for many years to assess memory in rodent model studies. Many of these studies consisted of correlating synaptic plasticity mechanisms with behavioral memory changes. To date, Transcranial Magnetic Stimulation (TMS) technology induces plastic changes in the human cortex, therefore, we set the aim to develop a Virtual Water Maze (VWM) task to conduct experimental research on human memory and design translational studies.

This work presents the development of an interactive graphical interface in which the user can navigate through a round pool in search of a hidden platform guided by four symbols presented in the pool's wall. During the different trials, the symbols and the platform remain in the same position, while the user appears in a random place within the pool. The user can move through the space using the arrow buttons on the keyboard and orientating the camera using the mouse. The data recorded from the videogame are: player's position coordinates (50 fps), time to complete each trial and time each signal is viewed.

We performed an experimental pilot study (2 male subjects, real/sham) in which we paired the VWM with simple TMS pulses towards the motor cortex following a Paired Associative Stimulation (PAS) protocol. While the subject is searching the platform oriented by the symbols, we programmed the trigger of a single-pulse TMS each time the user guides the camera towards a signal and it enters the field of vision. Therefore, we synchronized an activation of the motor cortex with the cortical endogenous activation of spatial memory process. We measured the baseline of memory capacity using VWM and the cortical excitability using Motor Evoked Potentials (MEPs), before, immediately after and 30-minutes after PAS.

The results unveiled a significantly potentiated spatial learning and motor corticospinal excitability in the experimental subject.

We have developed a VWM task to measure spatial memory in humans both for evaluation and induction of cortical plasticity.

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PS2-87

# The women neuroscientists disciples of Pío del Río-Hortega spread the Cajal School through Europe and America

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Pío del Rio-Hortega discovered microglia and oligodendroglia and he was, possibly, the most prolific mentor among all the direct disciples of Santiago Ramón y Cajal (Nobel laureate in Physiology or Medicine 1906, and considered as the father of modern Neuroscience). Among Río-Hortega´s mentees, there are three women, chronologically: 1) Pio's niece Asunción Amo del Río, technician specialized in the study of nervous system and specially neural tumours, who worked with Río- Hortega at Madrid, Valencia, Paris and Oxford from 1922 to 1939; 2) the distinguished Australian-born British pathologist Dorothy Russell, who also worked with Río-Hortega at Oxford (1939-40), where she completed her technical formation in the metallic impregnations, that started under Wilder D. penfield (the most distinguished disciple of Don Pío) to become one of the leaders in the field of Neuropathology and brain tumours after the death of Río- Hortega; and 3) Amalia Pellegrino de Iraldi, the last mentee in Río-Hortega´s career, at Buenos Aires, who develop most of her career as professor at the Universidad de Buenos Aires, after being the most distinguished collaborator of Eduardo De Robertis, and Arvid Carlsson (Nobel laureate in 2000), making fundamental contributions to the synaptic vesicles, cytoskeleton, and different `Hortegian´ subjects; among her disciples accounts Dr. Claudio Cuello (McGill University).

In the present work, we introduce and discuss the research and contributions of these women at Río-Hortega´s laboratory and thereafter for better comprehension of the History and its frame. The present work completes the contribution of women neuroscientists that worked with Cajal and his main disciples of the Spanish Neurological School.

PS2-88

# DOES RTP801/REDD1 PARTICIPATE IN tRNA METABOLISM?

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RTP801/REDD1 is a stress responsive protein overexpressed in neurons of patients with neurodegenerative disorders such as Parkinson's and Huntington's diseases. Its main function is to inhibit the mTOR pathway and therefore has a pro-apoptotic effect in differentiated cells like neurons. Nevertheless, RTP801 might have other functions not yet elucidated. In preliminary results from our laboratory, RTP801 was found to interact with HSPC117 and DDX1, two proteins that are part of the tRNA splicing ligase complex, which performs the ligation of the tRNA fragments generated during splicing. Since alterations in tRNA metabolism have recently been associated to the development of some neurodegenerative diseases, we aimed to deeper study the relationship between RTP801 and these tRNA-processing enzymes.

Here, we confirm by immunoprecipitation that RTP801 interacts with DDX1, which in turn interacts with HSPC117. Interestingly, we found that HSPC117 subcellular localization differs between wild type (WT) and RTP801 knockout (KO) mouse embryonic fibroblasts, being predominantly nuclear in the latter. Finally, we found that the levels of a neuron-specific tRNA are significantly reduced in the cortex of RTP801 KO mice compared to WT. These results suggest a novel role of RTP801 in tRNA processing, which must be further studied, as RTP801 could be a potential target to prevent altered tRNA metabolism in neurodegenerative diseases.

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PS2-89

# Small RNA in plasma extracellular vesicles as early biomarkers in Huntington´s disease

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Despite the toxicity of the mutant HTT protein in Huntington´s disease (HD) has traditionally been considered the main cause of the disease, growing evidence indicates that small CAG repeated RNAs (sCAG) and other perturbed small non-coding RNA (sRNA) are implicated in the pathogenesis. Extracellular sRNAs (exRNA) in body fluids can be found encapsulated in extracellular vesicles (EVs) and could act as toxic carriers. In HD, early diagnosis and prognosis biomarkers are needed for optimal clinical management, facilitating patients' stratification and characterization along the disease course and treatments. Specifically, the study of exRNA in plasma supposes a promising approach for harbouring biomarkers, as reflection of disease status. Here, we describe an optimal method for plasma-EVs purification by Size-exclusion chromatography (SEC) and Ultrafiltration (UF). We also explored EV-sRNA content providing a deep exRNA analysis. Profiling of plasma-EVs from three different cohorts, including manifest HD, premanifest HD and controls, revealed no differences in size and morphology of EVs. Instead, regarding EVs-exRNA, we show heterogeneous proportions of sRNAs biotypes distributions and distinct differential expression patterns profiles between groups. Using SeqCluster tool for sRNA analysis, we highlight that most sRNA-clusters in HD-EVs are downregulated in comparison to Control-EVs, with many changes occurring at premanifest stages. These findings suggest that alterations in circulating EV-sRNAs may reflect early clinical and pathological changes in HD patients.