Poster Session 5: Friday, 5th November, from 15:00 to 18:30, Exhibition Hall.

PS5-01

Identification of conserved neuron subtypes expressing Otp and Foxg1 in the extended amygdala of a lizard

Ms. Júlia Freixes[1,2], Dr Loreta Medina[1,2], Dr Ester Desfilis[1,2]
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The amygdala is a very complex structure, essential for emotion and social behavior. In particular, medial extended amygdala is involved in different aspects of social behavior (such as sexual, parental and aggressive behaviors). Research focused on its functional organization is important to understand the biological bases of the normal and pathologic development of social behaviors. The organization of this area is a consequence of two processes which act at different temporal scales: development and evolution. Using an evolutionary developmental neurobiology approach, our group recently identified a new embryonic domain at the transition between telencephalon and hypothalamus, that coexpress Otp and Foxg1, and produces most of the glutamatergic cells of the mouse medial extended amygdala. To investigate if this domain is also present in reptiles, we analyzed the expression of the transcription factors Otp and Foxg1, during brain development in the lacertid lizard Psammodromus algirus. Our results showed an area of Otp/Fogx1 expression overlap, with coexpressing cells that spread into the medial extended amygdala of P. algirus. This suggests the existence of a highly conserved neuron subpopulation in the medial extended amygdala of amniotes, and opens the venue to study its specific function and interaction with other neurons of the social behavior network. Funded by Ministerio de Ciencia e Innovación (PID2019-108725RB-100) and a Collaboration Fellowship in Research of the Ministerio de Educación (Beques de col·laboració universitària per al curs 2019-2020, COLAB 2019).

PS5-02

ROLE OF BASAL AUTOPHAGY IN THE REGULATION OF HIPPOCAMPAL NEURAL STEM CELL

Ms. Isabel Calatayud-Baselga[1], Mr. Jose María Guijarro[1], Dr. Lucía Casares-Crespo[1], Dr. Helena Mira[1]
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Two stem cell niches are still producing new neurons in the adult mammalian brain: the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampal dentate gyrus. Neural stem cells (NSCs) in these adult niches are preserved in a quiescent state. Dentate neural progenitors acquire a radial-glia like morphology and enter quiescence (qNSCs) during the early postnatal period. Later on, they regain proliferation in order to generate new neurons. The first step in neuronal production in the adult neurogenic niches is indeed the transition of qNSCs into an activate state (aNSCs). The implication of constitutive (basal) autophagy in the regulation of this transition in the mature brain and in NSC metabolism and protein quality control are beginning to be addressed.

In this work, we explored the role of the autophagy-lysosomal pathway in the maintenance of quiescence and in the regulation of proteostasis in NSCs from the SGZ. We performed in vitro experiments using NSCs in two different states: active or quiescent (4 days treatment with BMP4). Our results showed that quiescent cells have a higher overall protein content and more cytoplasmic protein aggregates. On the other hand, genome-wide microarray transcriptional analysis and RNAseq analysis showed an increase in the expression of genes related to the autophagy-lysosomal pathway in qNSCs vs. aNSCs. Moreover, not only the levels of autophagic proteins (LC3II, p62) are increased in qNSCs but also, there is a raise in the activity of autophagic-inducing kinases (AMPK, ULK1). Experiments with the autophagy inhibitor (Bacilomycin A1) and activator (Metformin) showed that basal autophagy is required to maintain the quiescent state. In addition, NSCs (Glast+ cells) prospectively isolated from mouse hippocampus at different postnatal ages allowed us to validate the in vitro findings.

In conclusion, our data demonstrate that basal autophagy is increased in qNSCs and that it has a role in the maintenance of quiescence. Currently, genetic and pharmacologic in vivo experiments are ongoing in order to complete this study.

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PS5-03

Postnatal refinement of interhemispheric callosal projections: GluN3A-mediated mechanisms

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During critical periods of brain development, synaptic and circuit refinement is driven by sensory experience. Both presynaptic and postsynaptic refinements involve loss and strengthening of synaptic contacts but how these processes are coordinated remains obscure. The non-canonical NMDA-receptor subunit GluN3A is thought to determine the timely remodelling of these circuits, but how it operates in specific brain circuits has not been addressed. Here we are investigating the roles of GluN3A in presynaptic and axonal refinement. We analyse interhemispheric callosal projection axons via in utero electroporation of the mouse somatosensory cortex with transgenic labelling. Analysis at different postnatal (P) days showed that initial extension and innervation of the contralateral cortex by callosal axons is not affected in GluN3A knockout (KO) mice with similar patterns to wild-type mice at P4 and P6. At P8, differences begin to arise in axon arbor density in layers 2/3 of the somatosensory S1/S2 border region, relative to other target layers. By P13, when a more mature configuration is reached, GluN3A KOs show a significantly different callosal axon cortical profile with arbors concentrating towards inner positions within L2/3 relative to wild-type that profusely innervate layer 1. This altered distribution of callosal axon arbors persisted at P20-22. Additionally, P13 and P20-22 GluN3A KOs display increased targeting in S2 as shown by the appearance of a second column displaying strong labelling. Ongoing experiments are testing for the cellular locus of GluN3A function within this circuit using specific manipulation in presynaptic or postsynaptic neurons in floxed-GluN3A mice lines. Potential candidate mediators of altered axonal refinement have been previously identified through RNA-seq experiments and some candidates show corresponding changes at the protein level. Future work involving chemogenetic and sensory deprivation approaches aims to determine activity and experience dependent roles within this GluN3A-affected axonal development.

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PS5-04

EFFECTS OF CHLORPYRIFOS ON CELL DEATH AND CELLULAR PHENOTYPIC SPECIFICATION OF HUMAN STEM CELLS

Ms. Andreea Rosca[1,2], Ms. Raquel Coronel[1], Ms. Rosa González[1,3], Ms. Patricia Mateos[1], Dra. López Victoria[3], Dra. María del Carmen González[4], Dra. Isabel Liste[1]

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Chlorpyrifos (CPF) is one of the most widely used organophosphate pesticide in agriculture. Inhibition of acetylcholinesterase is the best described mechanism for CPF neurotoxicity.

Chemical exposure during developmental stages can interfere with the proper development of the nervous system resulting in functional alterations or diseases during the lifespan of the individual and thus, resulting in developmental neurotoxicity (DNT). Despite the large body of results on animals, these studies are costly, time consuming and the results are not always reliable to assess the impact of chemical compounds on the developing human because animal models do not perfectly reflect human physiology. It remains clear that there is a growing necessity for developing alternative methodologies that can better identify and assess chemical substances with the potential to induce neurotoxicity during brain development and maturation.

Human stem cells are currently being a model that promises to be very useful in evaluating this type of toxicity and may be a valuable tool for DNT. In this study, the cell line hNS1 was used to evaluate the effects of CPF on early developmental stages. hNS1 cells were exposed to different concentrations of the pesticide and cell death, proliferation and cell fate specification were analyzed under differentiation conditions. The results showed that this compound induces apoptotic cell death at the highest doses tested. Besides, CPF promoted the differentiation of hNS1 cells into glial cells by increasing the pool of proliferating glia progenitors. This effect may be associated with a protective effect of glia against CPF.

In addition, we used brain organoids derived from human induced pluripotent stem cells (hiPSCs) to see if CPF has the same effects as in hNS1. We found that CPF induced cell death at the high dose tested and a decrease in the number of neurons and glial cells

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PS5-05

APC/C-Cdh1 inhibition promotes hypomyelination during postnatal development

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The E3 ubiquitin ligase APC/C-Cdh1 plays a key role in the developing brain, where it regulates the onset of neurogenesis during gestation (Delgado-Esteban et al, 2013). Whereas neurogenesis is complete at birth, synaptogenesis and myelination occurs during the postnatal brain growth. Recently, we described a novel human missense mutation in Cdh1 protein, which results in microcephaly, psychomotor retardation and refractory epilepsy (Rodríguez et al, 2019), alterations directly related to synapse dysfunction and hypomyelination (Repudi et al, 2021). Moreover, the APC/C-Cdh1 target, Rock2 (Bobo-Jiménez et al, 2017), negatively regulates myelination (Muñoz-Esquivel et al, 2019). Here, we study the role of APC/C-Cdh1 activity on oligodendroglial lineage and myelination in the postnatal brain.

We used Nestin-Cre Cdh1 conditional KO model by mating mice harboring a floxed allele of the Cdh1 gene with Nestin-Cre animals, which express Cre recombinase in neural cells from embryonic day 11. Oligodendrocyte, myelination and myelin sheath were analyzed by electron microscopy, immunohistochemistry, and western blotting.

Cdh1 deletion results in brain morphology alterations, mainly including microcephaly, severe hydrocephalus and ventriculomegaly, which becomes more pronounced during postnatal growth. Magnetic resonance T2 value at P21 (21 postnatal days) showed less cellular density and corpus callosum dysgenesis. In fact, Cdh1 cKO mice presented lower oligodendrocyte lineage cells in cerebral cortex, evidencing disorders in myelination process. Immunohistochemical Myelin Basic Protein (MBP) staining confirms corpus callosum agenesis and hypomyelination in P21 cortex. Moreover, P7 Cdh1 cKO mice presented less myelinated pons and midbrain areas, than wild-type mice, suggesting myelination delay. Finally, myelin ultrastructure analysis at P21 revealed decompacted and disrupted myelin sheath, compromising axon integrity.

Then, APC/C-Cdh1 activity regulates postnatal myelination, which highlights the impact of Cdh1 in the pathogenesis of neurodevelopmental myelin disorders.

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PS5-06

Amyloid Precursor Protein (APP) regulates cell fate specification in human Neural Stem Cells

Ms. Raquel Coronel[1,2], Ms Andreea Rosca[1], Ms Rosa González[1,3], Ms Patricia Mateos[1], Dra. Victoria López[3], Dr. Eduardo Arilla-Ferreiro[2], Dra. Isabel Liste[1]

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The pathological implication of Amyloid Precursor Protein (APP) in Alzheimer's disease has been widely documented due to its involvement in the generation of amyloid-β (Aβ) peptide. However, the physiological functions of APP are still poorly understood.

APP is a type I transmembrane glycoprotein widely expressed in the central nervous system (CNS) and is encoded by a single gene located on chromosome 21. Due to its role in a wide variety of processes, APP is considered by various authors as a multimodal protein. Specifically, APP seems to be implicated in neural development of CNS, playing a key role in the proliferation, differentiation, cell fate specification and maturation of neural stem cells (NSCs).

We have examined the endogenous APP expression in hNS1 cells, a model cell line of human NSCs, both under proliferation and throughout the differentiation period. Our results show elevated APP-immunoreactivity in hNS1 cells and, to investigate the potential function that APP plays in biology (proliferation, differentiation, cell fate specification and cell death) of human NSCs, we performed a loss-of-function study. To achieve the down-expression of APP, we used a commercial siRNA against human APP and we transfected it into hNS1 cells. Our data indicate that low levels of APP induce hNS1 cell fate towards a neuronal phenotype, while decreasing glial differentiation. Moreover, according our results, these effects could be, in part, mediated by β-catenin protein.

The knowledge of physiological functions of APP, as well as the possible signaling pathways that could be implicated, are essential to advance the understanding of the pathogenesis of AD.

PS5-07

EMBRYONIC CANNABINOID CB1 RECEPTOR KNOCKDOWN CONSEQUENCES IN GENE EXPRESSION AND FUNCTIONAL MATURATION OF PYRAMIDAL NEURONS

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Cortical development occurs by a series of proliferation and differentiation waves in a tightly regulated and coordinated process that ensures the appropriate formation of specific neuronal populations. Developing projection neurons migrate to their final layer location and after functional maturation and axon growth integrate in specific circuits. The endocannabinoid system exerts a neurodevelopmental regulatory role. Endocannabinoid production and CB1 receptor signalling regulates different processes including neural progenitor proliferation and identity, neuronal differentiation, and migration. Prenatal transient CB1 receptor knockdown causes alterations in neuronal morphology and interferes with radial migration, leading to greater seizure susceptibility in adulthood. To understand the consequences of defective embryonic CB1 receptor signalling in projection neuron development we performed gene expression analyses (microarray) of fluorescent FACS-sorted neurons at different times after siCB1 and control-siRNA in utero electroporation. In parallel we performed pathclamp electrophysiological analyses of delayed siCB1 neurons. We found that CB1 receptor knockdown induced gene expression changes with many downregulated transcripts involved in biological processes related to neurogenesis, axon growth and guidance, adherens junction, signalling mechanisms (PI3K/AKT/mTor signaling) and cell fate regulation. CB1 receptor knockdown neurons that migrated incorrectly, possess decreased firing frequency and less excitability, compared to control neurons. Ongoing studies aim to elucidate the causative gene expression changes responsible of defective neuronal maturation induced by CB1 signalling blockade. In summary, our findings describe the neuronal adaptations induced by cannabinoid CB1 receptor silencing at gene expression and functional level. The observed alterations of neuronal development have important implications for the understanding of neurodevelopmental disorders and the consequences of prenatal THC exposure.

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PS5-08

Proliferative rate and neurogenesis in human Neural Stem Cells are increased by Aβ40 peptide

Dra. Adela Bernabeu-Zornoza[1], Ms Raquel Coronel[1,2], Dra. Charlotte Palmer[1], Ms Rosa González[1,3], Ms Andreea Rosca[1], Ms Patricia Mateos[1], Dra. Victoria López[3], Dra. Isabel Liste[1]

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Amyloid-β 40 peptide [Aβ1-40 (Aβ40)] is present within the amyloid plaques in brains of patients with Alzheimer's disease (AD). Even though Aβ peptides are considered neurotoxic, they can mediate many biological processes both in adult brain and throughout brain development. However, physiological function of these Aβ peptides remains poorly understood, and existing data are sometimes controversial. Here we analyze and compare the effects of monomeric Aβ40 on the biology of differentiating human Neural Stem Cells (human-NSCs). For that purpose, we have used a model of human NSCs, called hNS1. Our data demonstrate that Aβ40 at high concentrations provokes apoptotic cellular death and damage of DNA in human NSCs while also increases the proliferation and favors neurogenesis in hNS1 cells by raising the percentage of proliferating neuronal precursors. These results provide evidence of how Aβ modulate/regulate human NSCs proliferation and differentiation, suggesting Aβ40 may be a pro-neurogenic factor. These data could contribute to a better understanding of the molecular mechanisms involved in AD's pathology and for the development of human NSC-based therapies for AD treatment, since these results could then be used in diagnosing the disease at early stages and be applied to the development of new treatment options.

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PS5-09

The cellular effect of Shh signaling in oligodendrocyte precursor cells (OPCs) depends on the microenvironment

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The morphogen Sonic Hedgehog (Shh) controls the proliferation of cells with stem cell properties in several regions of the CNS during embryonic and postnatal development, as well as in the adult[1]. The blockage of hedgehog signaling perinatal and in adult mice results in diminished expression of Gli1, reducing cell proliferation in vivo[2].

More recently the role of Shh signaling has been shown to be a critical pathway in the transition from neurogenesis to oligodendrogenesis in dorsal forebrain progenitors during late embryonic development[3]. Shh also regulates oligodendrocyte production in adulthood in the cortex and corpus callosum (CC). After focal demyelination induced by lysolecithin, the transcription of Shh target genes is increased[3], but Shh-expressing cells are not detected in the CC after chronic demyelination with cuprizone. However, the use of SAG (agonist of both canonical and non-canonical Hedgehog signaling pathways) increases the cell proliferation and enhances remyelination, but Gli1 fate-labelled cells in the CC do not change, which may indicate that is signaling through the non-canonical pathway[4].

Our present work shows the direct effect of Shh signaling on OPC proliferation and myelination. To do this, we crossed the NG2-CreERT2TdT mice with both SmoM2 and Smofl/fl lines and studied the gain and loss of function of smoothened receptors implicated in the canonical and non-canonical pathways. We also provide evidence that Shh synergizes with PDGFAA signaling in the modulation of OPC proliferation in vitro from postnatal and adult cortex.

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PS5-11

In vivo astrocyte activation modulates spontaneous inhibitory activity during slow wave oscillations in the somatosensory cortex

Dr. Salvador Herrera-Pérez[1], Ms Claudia Miguel-Quesada[1], Ms Marta Zaforas[1], Ms Elena Alonso-Calviño[1], Ms Elena Fernández-López[1], Dr. Juan Aguilar[1], Dra. Juliana M Rosa[1]
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During sleep and anesthesia, cortical spontaneous activity is dominated by slow wave oscillations (SWO, <1.5 Hz) consisting of alternating synchronized network activity (up-states) and generalized neuronal silence (down-states). Several evidence indicate distinct excitatory and inhibitory neuronal mechanisms involved in the SWA regulation in rodents. Nonetheless, in vitro and in vivo data indicate astrocytes as regulators of cortical up-states by controlling both the initiation and the frequency of synchronized oscillations. However, whether astrocytes are also able to regulate neuronal excitability during up-states or are involved in the mechanisms of down-states is still unknown. Here, we investigated the role of astrocytes in the spontaneous cortical oscillatory activity by using a combination of in vivo electrophysiology and pharmacogenetics. For that, a 32-channel multielectrode was lowered into the somatosensory cortex to record spontaneous neuronal activity, while astrocyte modulation was achieved by using a hM3Dq-Gq-DREADD under the astrocyte GFAP promoter and acute i.p. injection of its ligand clonazepine (CNO). Neuronal recordings obtained from the same animals before and 1-hour after CNO application showed that astrocyte activation exhibited a clear effect on the SWO neuronal firing. While firing rate during down-states was significantly enhanced, up-states presented a reduced spontaneous activity. To determine the neuronal cell-type modulated by astrocytes under our conditions, we used a spike-sorting clustering algorithm based in three measurements (width, Trough-to-peak and after-high-hyperpolarization). Our analysis showed that CNO increased the number of putative inhibitory neurons during down-states, without affecting the number of putative excitatory clusters. Such apparent enhancement of inhibitory activity shorten down-state duration and therefore increasing SWO power as well as induced a slower down-to-up transition and decreased up-state amplitude. In conclusion, our findings indicate that down-states in SWO are directly modulate by astrocytes. In addition, the appearance of new putative inhibitory clusters would suggest the modulation of GABAergic interneurons by astrocyte activity.

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PS5-12

Adaptative myelin plasticity linked to increased neuronal excitability in the somatosensory cortex

Ms. Claudia Miguel Quesada[1], Ms. Alba Fernández-González[1], Dra Elvira Brocca[1], Dr Alonso Higuero[1], Ms. Marta Zaforas[1], Ms Elena Alonso-Calviño[1], Ms Elena Fernández-López[1], Doctor José Abad[1], Doctor Juan Aguilar[1], Dra Juliana M Rosa[1]

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The neocortex is organized in vertical columns responsible to integrate and compute signal information. In addition to that, distinct layers within the vertical organization project horizontally to neighbouring columns in order to distribute activity between cortical areas. Interestingly, recent anatomical data shows that horizontal axonal projections, specially the long-ones in L2/3, exhibit increased myelin segments elongation following monocular deprivation. Such adaptive myelin plasticity may improve synaptic efficacy of corticocortical connections with a possible role in mediating the reorganization of cortical maps after sensory deprivation. Here, we explored the relationship between axonal myelination and the level of cortical reorganization in distinct layers of the somatosensory cortex following central sensory deprivation. Furthermore, we also investigated the ability of astrocytes, known to provide trophic factors for myelinating glia, to influence the adaptive myelin plasticity. Complete thoracic spinal cord was used to induce sensory deprivation of the cortical areas receiving information from hindlimbs. Fifteen-to-thirty days later, injured and control animals were subjected to electrophysiological recordings using a vertical array lowered into the hindlimb cortex to record evoked potentials in response to contralateral forelimb stimulation. Our experimental design aimed to determine the strength of the synaptic connectivity between the deprived and intact cortex. Our data showed that sensory deprivation enhanced L2/3 corticocortical connectivity observed as increased magnitude and slope of deprived neurons. Next, we explored whether the increased L2/3 synaptic efficacy was associated to myelin remodelling. While immunostaining against the neurotrophic factor-oligo2 showed no overall changes in both deprived and intact cortices, myelin basic protein staining showed increased intersections and longitudinal myelination patterns. These changes were not observed in IP3R2-/- mice exhibiting deficient astrocyte activity, suggesting that astrocytes directly impact myelination. Overall, our data indicate a positive correlation among neuronal excitability and adaptive myelin plasticity that may mediate cortical reorganization through increased L2/3 corticocortical connectivity.

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PS5-13

Cortical astrocytes exhibit functional heterogeneity to discriminate sensory modalities

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Layer-specific activity of cortical circuits critically depends on the interplay among distinct cell types to shape sensory stimulus selectivity and control gain. In this complex network, astrocytes are crucial as they can sense the synaptic activity within the layering circuits to modulate the strength and timing of both excitatory and inhibitory neurons. However, cortical laminar distribution of astrocytes does not correspond to the six excitatory neuronal layers, which leads to the question on whether astrocytes across cortical layers may exhibit functional heterogeneity or engage in different interactions with neighbouring neurons to modulate neuronal dynamics of sensory processing. Here, we used a combination of in vivo electrophysiology, behavior and genetic tools to explore the layering functional organization of astrocytes as well as their ability to modulate the layer-specific neuronal circuitries. By using brain slices injected with the AAV5-gfaABC1D-cyto-GCaMP6f, we found that astrocyte activity is inherently distinct across cortical layers, with L2/3 astrocytes being less excitable and L5/6 exhibiting higher number of spontaneous oscillations. To determine whether such astrocyte functional diversity play a role in the neuronal sensory processing and stimulus selectivity, we used in vivo electrophysiology to record neuronal evoked-potentials across all layers and sensory behavioral tests while modulating astrocyte activity. Up-regulation of astrocyte activity using GFAP-hM3D(Gq)-DREADD decreased evoked-potential magnitudes in response to high-stimulus intensity in L4/5/6 neurons, which was accompanied by an increase threshold of paw withdrawal following thermal stimulation. On contrary, astrocytes down-regulation using IP3R2-/- mice line decreased L2/3/4 evoked-potential in response to low intensity stimulation and consequent increased threshold in response to tactile stimuli. Therefore, our data indicates that astrocytes work as a buffer of neuronal activity by plausible controlling E:I balance in a stimulus-dependent manner. In addition, astrocyte functional heterogeneity may serve to control stimulus sensitivity in a layer-dependent manner with consequences in behavior output.

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PS5-14

Neuron-derived extracellular vesicles enhance synaptic plasticity through RTP801

Ms. Julia Solana Balaguer[1,2,3], Mr. Albert Coll Manzano[1,2,3,4], Mr. Genís Campoy Campoy[1,2,3], Dr. Leticia Pérez Sisqués[1,2,3], Dr. Núria Martín Flores[1,2,3,5], Dr. Jordi Alberch[1,2,3,4], Dr. Jordi Soriano[1,6], Dr. Mercè Masana[1,2,3,4], Dr. Cristina Malagelada[1,2,3]

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Neurodegenerative diseases are characterized by an impairment in synaptic plasticity leading eventually to cognitive symptoms in patients. Extracellular vesicles (EVs), which are involved in intercellular communication, have been described to have an important role in synaptic plasticity, as they are carriers of bioactive miRNAs, proteins and lipids. These molecules are involved in synaptic processes and can influence firing rate in the recipient neurons. RTP801/REDD1 is a pro-apoptotic protein which levels are elevated in compromised neuronal populations from patients with neurodegenerative disorders.

The aim of this study is to examine how RTP801 modulates the synaptic effect of EVs at structural and functional levels.

EVs were isolated by ultracentrifugation from rat cortical neurons at DIV13 and used to treat other cultured cortical neurons for 24h. We next examined synaptic plasticity at several levels, assessing the number of consolidated synapses using PSD-95/VGLUT-1 contacts as readout, by immunofluorescence; measuring the levels of synaptic proteins in total neuronal lysates by western blot and investigating whether EVs could change individual neuron activity or collective events, including the topology of the neuronal network.

We next studied how the lack of RTP801 affects synaptic plasticity treating rat cortical cultures with EVs obtained from WT or RTP801 KO mouse cultured neurons.

We found that neuron-derived EVs enhance the consolidation of glutamatergic synapses in recipient neurons, effect that is lost with EVs isolated from RTP801 KO neurons. Moreover, our preliminary results suggest that RTP801 modulates synaptic plasticity by affecting the EVs content.

Further studies will be needed to frame RTP801 as a transcellular mediator of neurodegeneration and to put neuronal EVs in the spotlight to prevent synaptic plasticity impairment.

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PS5-15

Microglial local translation in Aβ-induced pathology

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Protein synthesis is essential for the maintenance of cellular proteostasis. Neural cells (e.g neurons, astrocytes, oligodendrocytes) are highly polarized and therefore their proteins have to be asymmetrically distributed to fulfil their function. This distribution occurs through two different mechanisms: 1) the classical pathway where proteins are synthetized in the perinuclear region and delivered to their target site after maturation and/or 2) through local translation, where mRNAs are transported to the target site in a repressed state to be locally translated into proteins.

Local translation allows cells to react in spatial and temporal manner to numerous stimuli. Most data regarding local translation have been obtained in neurons. However, there is evidence that local translation plays a crucial role in other CNS cell types too. For instance, local translation of MBP in oligodendrocytes has been described in neurodegenerative conditions. More recently, the ability of peripheral astrocytic proteins to translate proteins has been described.

Microglia, although not being of neural origin, are the resident immune cells of the nervous system, and show a morphology as equally complex as neurons and neuroglia. In microglia, local translation has newly been described. Nonetheless, the involvement of local translation in these cell types in physiology and pathology is still to be elucidated. Taking into account that glial cells might be active participants in neurodegenerative diseases and based both on the literature and recent results of our group, our hypothesis is that local translation in microglial peripheral processes is involved in neurodegenerative diseases.

Previously, our group has obtained results supporting the idea that local translation in microglia is altered in the context of inflammation. It is well stablished that neurodegeneration and neuroinflammation are strictly related. Thus, we are currently analysing the effect of both parameters combined and their relation to changes in local translation of microglial peripheral processes.

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PS5-16

Organization of a Sox2-positive glial cell population in the optic nerve associated with growing fibers in the fish visual system

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The visual system of teleost fish shows growth and regeneration capacities during the entire animal's life. Therefore, the pre-encephalic visual system [retina, optic nerve head (ONH), and optic nerve (ON)] of adult fish serve as a model for studying neurogenesis and regeneration of the vertebrate central nervous system (CNS). Previous work has shown differences of Sox2 expression in areas of pre-encephalic visual system, which indicates that this transcription factor could have several functions in the CNS. Our study focused on a detailed characterization of a Sox2 positive cell population located in the first portion of the optic nerve. We have used adult specimens of the cichlid fish Astatotilapia burtoni as an animal model, which shows substantial growth adding retinal tissue and optic nerve fibers throughout life. Clearing samples of pre-encephalic visual system (the whole eye with an optic nerve piece), and immuno staining, we identified a population of glial cells positive for Sox2. These cells are arranged around the axons from newborn neurons identified by staining for doublecortin and location in the optic nerve. Our results suggest that this glial population is associated with the pathway navigation of the new axons from the retina. Besides known functions in stem cell pluripotency, Sox2 could be involved in neurochemical signaling and/or a pool of potential proliferative cells, in possible combination with other regulatory factors, in the fish visual system. Understanding the variety of cell types and subtypes in the visual system of fish and their plasticity could be the key to comprehend the growing and regenerating processes in the adult vertebrate CNS.

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PS5-17

Reactive neural stem cells and aberrant neurogenesis in a neuron-specific model of Dravet Syndrome

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Hippocampal neurogenesis (HN) is a form of neuroplasticity which implicates the generation of new neurons from neural stem cells (NSCs) in the dentate gyrus (DG). Although HN persists throughout adulthood, it reaches maximum values during early postnatal periods, when the population of NSCs is at its largest.

NSC activity and HN are particularly regulated by neuronal activity and severe alterations have been found in the hippocampal neurogenic niche in mouse models of epilepsy. Induction of reactive-like and gliogenic NSCs (React-NSCs) besides aberrant neurogenesis, defined by altered newborn neuron morphology, migration and functional properties, are induced by epileptic seizures.

We are thus interested in Dravet Syndrome (DS), a severe form of infant epilepsy characterized by the early onset (3-6 months of age) of seizures. DS is caused by mutations in the Scn1a gene encoding the α1 subunit of sodium channel Nav1.1, and provokes febrile seizures, hyperexcitability, neurological comorbidities and premature death. Therefore, we hypothesize that early seizures could have a greater impact and longer-lasting on the neurogenic niche in DS due to their early onset.

Through confocal microscopy imaging we are analysing the neurogenic niche of a novel inducible knock-in mouse model of DS (Syn-Cre/Scn1aWT/A1783V) at postnatal day 25 (soon after the onset of seizures) which consist in the neuron-targeted expression of a missense mutation (A1783V) in the Scn1a gene. We have observed the induction of React-NSCs, characterized by more and thickened branches plus overproliferation. We have also observed a strong induction of aberrant neurogenesis. Newborn immature neurons, identified by the expression of doublecortin are present in much higher numbers; migrate abnormally towards the hilus and the molecular layer; and have basal dendrites and V-shaped proximal apical dendrites. We are currently investigating other possible alterations such as cell death/survival, differentiation imbalance and changes in astroglia and microglia.

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PS5-18

Intact induction and presynaptic occlusion of short and long-term potentiation in synaptophysin family knockouts

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Synaptophysin family proteins are ubiquitous integral components of synaptic vesicle membranes. We recently found that baseline synaptic strength is enhanced in quadruple knockouts missing all four family members owing to elevated probability of release of the docked and primed readily releasable vesicles within presynaptic terminals. Deficits in both short- and long-term potentiation were detected previously in partial mutants missing one or two family members, and are more severe in the quadruple knockouts. The short-term deficits could result from the elevated baseline probability of release because: (1) short-term potentiation is also caused by elevated probability of release; and (2) a previous study identified a limit that would occlude further elevations if unaltered in the mutants. In contrast, long-term potentiation is widely thought to be caused by a different type of mechanism. Nevertheless, here we show that the deficit in long-term potentiation can be rescued by lowering extracellular calcium, which lowers the baseline amount of release back to wildtype levels. The result suggests that the most widely studied form of long-term potentiation is caused by elevated probability of neurotransmitter release from presynaptic terminals, and that the amount of potentiation can be limited by a native occlusion mechanism that was previously shown to heavily influence the timing of recovery from short-term depression.

PS5-19

Parallel processing of quickly and slowly mobilized reserve vesicles in hippocampal synapses

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Neurotransmitter in presynaptic terminals is stored within synaptic vesicles, and is released into the synaptic cleft via exocytosis. However, a synaptic terminals contains hundreds of vesicles in the interior, whereas fewer than ten can dock at once to the active zone area of the plasma membrane where exocytosis occurs. The vesicles in the interior are thought to be held within so called reserve pools, but the concept of a pool remains poorly defined. Here we use optical imaging dyes and a combination of low and high frequency stimulation to confirm that individual hippocampal presynaptic terminals in cell culture contain multiple reserves that can be distinguished functionally by how quickly the contents can be mobilized for exocytosis. Quickly and slowly mobilized reserves were mobilized in parallel, and did not mix, even during heavy stimulation. The results are not consistent with long-standing models where reserve pools are connected in series, but instead support an alternative that emerged from a series of previous electrophysiology studies, where: 1) active zones contain multiple independent docking/release sites; (2) the release sites vary in probability of catalyzing exocytosis following individual action potentials; and (3), each docked vesicle is connected to a separate reserve.

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PS5-20

Galectin-3 impairs gamma oscillations at hippocampal CA3 area ex vivo: A suitable target to counteract the progression of Alzheimer's disease

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Alzheimer's disease (AD) is a progressive multifaceted neurodegenerative disorder for which no disease-modifying treatment exists. Cognitive decline is a clinical hallmark of AD, and its severity correlates with the level of disruption of neuronal networks activity. Recently, neuroinflammation has been revealed central to the pathology progression with evidence suggesting that microglia-released galectin 3 (gal3) plays a pivotal role amplifying neuroinflammation in AD. However, possible involvement of gal3 in the disruption of cognitive-relevant neuronal network oscillations remains unknown. Here we investigated the functional implications of gal3 for neuronal network functioning by performing ex-vivo recordings of fast electrical rhythmic activity within gamma frequency range (gamma oscillations, 20-80Hz) in CA3 area of WT hippocampal mice brain slices. Gamma oscillations were induced by applying 100 nM KA either in an interface- or submerged-type recording chambers. Concomitantly to local field potential we performed patch-clamp recordings of relevant neuronal populations (fast-spiking neurons (FSN) and pyramidal cells (PCs)) with focus on FSN. We used two different general approaches (1) gamma induced after gal3 treatment and (2) gal3 application during ongoing gamma oscillations. We observed that gal3 application significantly decrease gamma oscillation power and rhythmicity which is mediated by the gal3-carbohydrate-recognition domain and prevented by the gal3 inhibitor TD139 in a dose-dependent manner. Such disruption resulted to be activity-dependent and was accompanied by the impairment of FSN- and PC-gamma phase-locking. Interestingly, TD139 also prevented Aβ42-induced degradation of gamma oscillations. Notably, we found that gamma oscillations are impaired at CA3 hippocampal area of 5xFAD mice model at 6 months old while gamma oscillations recorded from 5xFAD mice lacking gal3 (5xFAD-Gal3KO) remain similar to age-matched WT counterpart. Thus, we report for the first time that gal3 impairs cognitive-relevant neuronal network dynamics. Moreover, our findings suggest that removing/inhibiting gal3 could be beneficial to counteract the neuronal network instability typical of AD.

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PS5-21

Differential effects of Paraquat in human and mouse astrocyte's membranes.

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During last decades it has been observed an increasing prevalence in ageing concomitant diseases; a longer life expectancy due to an improvement of life conditions is the main factor of this augmentation. As astrocytes are responsible for proper neuronal function, their importance is clear to the maintenance of brain health. Metabolism homeostasis alterations, such as oxidative stress, can trigger these conditions, producing cellular pathological changes as lipid peroxidation, oxidative modification of proteins and DNA damage.

One of the main mechanisms involved in cellular oxidation is Reactive Oxygen Species (ROS) formation, key deregulators of cellular stability. ROS can be produced by mitochondrial electron transport chain dysregulation by external pro-oxidant compounds action, such as Paraquat.

To study sex influence, species and paraquat exposure on the activity of mitochondrial respiratory chain in astrocytes of different species, we developed microarrays using cell membranes isolated from a human astrocytic cell line (1321N1) and primary cultures of male and female mouse astrocytes. Subsequently, the superoxide formation capacity of each sample was determined on cell membrane microarrays using complex I substrate (NADH) combined with specific inhibitors of mitochondrial complex I (rotenone), complex III (antimycin A) and complex IV (azide). Paraquat treated astrocytes showed a higher superoxide formation when compared with control group, not only in basal condition but also in presence of respiratory inhibitors. A significant difference between male and female was also observed in mouse astrocytes primary cultures, while no difference was detected between human and mouse in male astrocytes.

Furthermore, the difference seen between control and paraquat-treated human astrocytes was not only due to mitochondrial electron transport chain, but also other NADH oxidoreductases might be implicated in ROS generation. Thus, further investigation with specific protocols will be necessary to elucidate it. How astrocytes manage oxidative stress and ROS formation is central to their neuroprotective responses.

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PS5-22

Role of lysophosphatidic acid receptor LPA1 in use-dependent short-term depression and recovery at excitatory synapses in rat hypoglossal motoneurons

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The bioactive phospholipid LPA impacts excitatory synaptic strength in hypoglossal motoneurons (HMNs) by a LPA1-mediated presynaptic mechanism influencing neurotransmitter release (PLoS Biol. 2015 13(5):e1002153). Here, we hypothesized that use-dependent short-term plasticity at excitatory synapses engages, at least in part, LPA-LPA1 signaling. In brainstem slices from rat pups (P5-P9), a high frequency stimulation (HFS, @20-Hz, 60-s) protocol was applied to the ventrolateral reticular formation and excitatory postsynaptic currents (EPSC) from HMNs were analyzed during and after (@0.2-Hz) HFS. Exogenous application of LPA (1 □M), but not vehicle, to the bath solution altered synchronic and asynchronic neurotransmitter release during HFS. The asynchronic component is known to increase during the train by accumulation of presynaptic [Ca2+]i. Furthermore, LPA delayed EPSC recovery after HFS. Addition to the bath solution of the LPA1 inhibitor AM095 (10 □M) or preceding microinjection of a small-interfering RNA against lpa1 (siRNAlpa1) into the fourth ventricle at P4, both affected synchronic and asynchronic release in an opposite direction that LPA. A non-interfering siRNA was taken as control in siRNAlpa1 experiments. AM095 and siRNAlpa1 both accelerated EPSC reestablishment after HFS. Finally, addition of a non-permeable Ca2+-chelator EGTA (11 mM) into the internal solution of the recording pipette or permeable AM-EGTA (300 □M) to the bath solution, differentially effected AM095-induced alterations on EPSCs during and after HFS. Altogether, these outcomes indicate that LPA-LPA1 signaling mediates short-term depression and recovery kinetics during and after HFS, respectively. The mechanism of action of endogenously synthesized LPA seems to depend on both pre- and post-synaptic [Ca2+]. A more detailed analytical processing is needed to clarify particular synaptic events regulated by this signaling pathway in use-dependent synaptic plasticity.
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Keywords: Motoneurons, Lysophosphatidic acid, short-term synaptic plasticity.

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PS5-23

p11 (S100A10) knockdown impacts synaptic strength and use-dependent short-term plasticity at excitatory synapses in rat hypoglossal motoneurons

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Chaperone p11 (S100A10) is an adaptor protein that regulates trafficking and plasma membrane expression of several ion channels and receptors. Thus, p11 sets up motoneuron (MN) intrinsic excitability (Nat Commun. 2019;10(1):3784). Although there is evidence supporting a presynaptic role of p11 in synaptic dynamics, little evidence exists so far on its involvement in neurotransmission and synaptic plasticity. In brainstem slices from rat pups (P7-P9), a high frequency stimulation (HFS, @60-Hz, 10-s) protocol was applied to the ventrolateral reticular formation and excitatory postsynaptic currents (EPSC) from hypoglossal MNs (HMNs) were analyzed during and after HFS. A small-interfering RNA against p11 (siRNAp11; 5 □g/5 □l) was injected into the fourth ventricle at P5, taken administration of a non-interfering siRNA (cRNA) as control. siRNAp11 reduced (-56.6 ± 5.2%) mRNAp11 expression in brainstem of P7-P9 rats. P11 knockdown was accompanied by a reduction in the amplitude of recorded EPSCs (cRNA: 0.467 ± 0.056 nA; siRNAp11: 0.338 ± 0.048 nA). Interestingly, siRNAp11 altered both synchronic and asynchronic neurotransmitter release during HFS. Whilst the kinetic of reduction in charge transfer for the synchronic component of the synaptic response across the train experienced only a subtle delay after p11 knockdown, the asynchronic component was strongly attenuated by this treatment (cRNA: 1.58 ± 0.372 nC; siRNAp11: 0.66 ± 0.119 nC). Since the asynchronic component increases during train by accumulation of presynaptic [Ca2+]i, siRNAp11-induced reduction in this component also supports a pre-synaptic site of action of endogenous p11. Kinetic of EPSC recovery after HFS was also altered in siRNAp11 relative to cRNA-treated pups. A more detailed analytical processing is needed to clarify particular synaptic events regulated by this protein in use-dependent synaptic plasticity.
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Keywords: Motoneurons, S100A10, short-term synaptic plasticity.

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PS5-24

Molecular mechanisms underlying NMDA receptor-BK channel coupling in specific brain regions

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Postsynaptic N-methyl-D-aspartate receptors (NMDARs) play a crucial role in excitatory synaptic transmission and plasticity, but their role must be framed into a more complex physiological picture, where they can interact with other ion channels shaping their function. A rather unexplored partnership is that of NMDAR with large-conductance calcium- and voltage-gated potassium (BK) channels, which until now had been exclusively studied in granular cells of the olfactory bulb and hippocampal pyramidal neurons. In these neuronal types, their expression seems restricted to the soma, regulating cellular excitability. We have recently shown that synaptic NMDAR–BK coupling occurs in a subpopulation of barrel cortex layer 5 pyramidal neurons, where it is promoted by a physical proximity maximizing NMDA receptor calcium access to the BK channel. This proximity allows a negative feedback mechanism to significantly and selectively filter plasticity, providing input-specific synaptic diversity to the thalamocortical circuit (Gomez et al, 2021, https://doi.org/10.1101/2020.12.30.424719). Using a panel of biophysical, cellular and imaging techniques in brain slices and heterologous expression systems, we now describe this mechanism in other brain areas and study the role of specific NMDAR and BK subunits in this coupling mechanism.

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PS5-25

Dissociation of functional and structural plasticity of dendritic spines during NMDAR and mGluR-dependent long-term synaptic depression in wild-type and fragile X model mice

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Many neurodevelopmental disorders are characterized by impaired functional synaptic plasticity and abnormal dendritic spine morphology, but little is known about how these are related. Previous work in the Fmr1-/y mouse model of fragile X (FX) suggests that increased constitutive dendritic protein synthesis yields exaggerated mGluR5-dependent long-term synaptic depression (LTD) in area CA1 of the hippocampus, but an effect on spine structural plasticity remains to be determined. In the current study, we used simultaneous electrophysiology and time-lapse two photon imaging to examine how spines change their structure during LTD induced by activation of mGluRs or NMDA receptors (NMDARs), and how this plasticity is altered in Fmr1-/y mice. We were surprised to find that mGluR activation causes LTD and AMPA receptor internalization, but no spine shrinkage in either wildtype or Fmr1-/y mice. In contrast, NMDAR activation caused spine shrinkage as well as LTD in both genotypes. Spine shrinkage was initiated by non-ionotropic (metabotropic) signaling through NMDARs, and in wild-type mice this structural plasticity required activation of mTORC1 and new protein synthesis. In striking contrast, NMDA-induced spine plasticity in Fmr1-/y mice was no longer dependent on acute activation of mTORC1 or de novo protein synthesis. These findings reveal that the structural consequences of mGluR and metabotropic NMDAR activation differ, and that a brake on spine structural plasticity, normally provided by mTORC1 regulation of protein synthesis, is absent in FX. Increased constitutive protein synthesis in FX appears to modify functional and structural plasticity induced through different glutamate receptors.

PS5-26

Astrocyte-mediated switch in spike timing dependent plasticity during hippocampal development

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Presynaptic spike timing-dependent long-term depression (t-LTD) at hippocampal CA3-CA1 synapses is evident until the 3rd postnatal week in mice, disappearing during the 4th week. At more mature stages, we found that the protocol that induced t-LTD induced t-LTP. We characterized this form of t-LTP and the mechanisms involved in its induction, as well as that driving this switch from t-LTD to t-LTP. We found that this t-LTP is expressed presynaptically at CA3-CA1 synapses, as witnessed by coefficient of variation, number of failures, pairedpulse ratio and miniature responses analysis. Additionally, this form of presynaptic t-LTP does not require NMDARs but the activation of mGluRs and the entry of Ca2+ into the postsynaptic neuron through L-type voltage-dependent Ca2+ channels and the release of Ca2+ from intracellular stores. Nitric oxide is also required as a messenger from the postsynaptic neuron. Crucially, the release of adenosine and glutamate by astrocytes is required for t-LTP induction and for the switch from t-LTD to t-LTP. Thus, we have discovered a developmental switch of synaptic transmission from t-LTD to t-LTP at hippocampal CA3-CA1 synapses in which astrocytes play a central role and revealed a new form of presynaptic LTP and the rules for its induction

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Adenosine Receptor-Mediated Developmental Loss of Spike Timing-Dependent Depression in Layer 4 to Layer 2/3 synapses of Somatosensory Cortex

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Spike timing-dependent plasticity (STDP) is a Hebbian learning rule important for synaptic refinement during development and for learning and memory in adults. Presynaptic spike timing-dependent long-term depression (t-LTD) exists in layer 4 to layer 2/3 synapse of somatosensory cortex, which is present until the 4th postnatal week in mice, disappearing at the end of this 4th (P13-P27) week of development. We were interested in the mechanisms underlying this developmental loss of t-LTD. We have found that t-LTD is recovered when adenosine A1Rs are antagonized at P28-P37, whereas it´s induction is prevented at P13-P27 by activating A1Rs. Furthermore, we found that the adenosine that mediated the loss of t-LTD is supplied by astrocytes, as when astrocytes are treated with the Ca2+ chelator BAPTA, t-LTD is recovered at P28-P35. Similarly to STDP, pairing the stimulation of astrocytes with EPSPs at P13-P27 induces LTD, but not at P28-P37. These results provide direct evidence for the mechanism that closes the window of plasticity associated with t-LTD, revealing novel events probably involved in synaptic remodeling during cortical development.

PS5-28

Astro-Light: a new tool for modulation of specific astrocytic networks

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Unravelling the principles of information processing in complex cell circuits requires techniques capable of target and modulate specifically the activity of those elements involved. Although it has been demonstrated that astrocytes play an active role in neuronal transmission, the evolution of genetic tools to study and control these circuits has focused mainly on neuronal activity. Currently, there are available techniques to modulate astrocytic activity with precise temporal control (optogenetics), or in a sustained activation period (chemogenetics). Nevertheless, these tools act on the whole astrocytic population and it remains challenging to target gene expression or activity in specific populations of astrocytes, leaving the role of these cells in neural circuits or behaviour still unclear.

In this study, we present a new tool to translate the activity-mediated calcium signals of astrocytes into gene expression in a light-dependent manner, i.e. Astro-Light. Using a combination of electrophysiology, molecular, pharmacological and behavioural techniques, we have tested Astro-Light capacity to modulate the activity of specific astrocytic networks with implications in animal behaviour.

First, we engineered Astro-Light vectors under GFAP promoter and characterized Astro-Light expression after viral infection in the mouse Nucleus Accumbens (NAc). We apply Astro-Light to label astrocytes in the NAc that are activated during optogenetic stimulation of long-range excitatory inputs thought to regulate motivated behaviors. Finally, we tested the ability of Astro-Light to modulate animal behaviour.

Our results reveal Astro-Light as a functional and powerful tool for studying astrocyte-neuron interactions and enables dissection of astrocytic circuits underlying complex behaviors with high spatiotemporal precision.

PS5-29

The olfactory peduncle in human and nonhuman primates

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The human olfactory system has historically been considered a system primarily involved in odor recognition. However, during the last decade, olfactory dysfunction has been studied as a preclinical and prodromic symptom related to Parkinson's and Alzheimer's diseases. The olfactory system appears to act as direct pathway to other cortical olfactory regions of the brain for some pathogens or prion-like diseases, and the anatomy of sensory neurons, directly exposed to the environment in the nasal cavity, allows this. In addition, most mammals generate new neurons during adulthood that are incorporated into a pre-existing olfactory circuit, presumably to keep their functionality intact. However, in adult humans this process has not been clearly elucidated and information regarding cytoarchitecture and cellular composition of different olfactory structures in the olfactory peduncle are still scarce.

In this work, we studied 28 olfactory nerves from humans aged 19-93 years and 5 cases from young adult primates (Macaca fascicularis). The olfactory tract of both species was dissected into the main olfactory bulb and anterior, medial and posterior regions of the olfactory peduncle. Then, morphology and cytoarchitecture were studied and compared. For this purpose, coronal section micrography atlas of the human olfactory tract has been developed. We observed an anatomic variation along the different portions and different cell distribution layers. Electron microscopy, immunohistochemical, and confocal techniques were performed to confirm the distribution of cell populations, such as glia, mature and young putative neurons and undifferentiated cells in the olfactory peduncle of both species. We also evaluated the density and distribution of blood vessels and corpora amylacea. Furthermore, in M. fascicularis, a rostral migratory stream (RMS) was identified in all cases along the peduncle and migrating neuroblast cell populations were stereologically quantified. These data aim to shed light on the differences in these olfactory structures between both species, the relationship between adjacent structures and the putative effect of aging on the human adult neurogenic process.

KEYWORDS: Olfactory system, adult neurogenesis, primates, humans, olfactory peduncle, doublecortin,

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PS5-30

STUDY OF THE DISTRIBUTION OF □-TTP AND CALCIUM BINDING PROTEINS IN THE HIPPOCAMPUS OF A MURINE MODEL OF DELAYED AGEING, THE POL μ MOUSE.

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Aging is a physiological and multifactorial process, where inflammatory mechanisms and oxidative stress (OS) play a fundamental role and leading to a gradual loss of the functionality of the different organs and tissues. Several neuron populations are selectively affected by the aging process. Interneurons play a key role in the maturation, function, plasticity, and organization of cortical circuits, as well as in the control of the activity of major or principal neurons. Disturbances in the hippocampal-inhibiting networks, which involve the loss of specific subpopulations of GABAergic interneurons (INs), could be an important factor in hippocampal aging. In recent years, the effects of antioxidant supplementation through the diet have been studied as it has been proved to reduce the redox imbalance and to decrease the effects of OS on aging. Vitamin E (VitE) is one of the antioxidants more widely used as an antioxidant therapy. Of all the isomers that constitute the VitE, the organism preferentially retains the isomer configuration α-tocopherol (α-T), introduced into neurons by a specific protein, the α-tocopherol transfer protein (α-TTP), widely distributed throughout the brain. This is one of the most affected organs in aging, and the hippocampus, mainly responsible for the generation and recovery of memories and spatial orientation, has been described as an especially vulnerable area. We have studied in detail the expression of α-TTP in all the regions and layers of the hippocampus along aging, as well as the presence of this transfer protein in different INs populations. The analysis was made in Pol □□mice, a delayed-ageing model, in animals of 4 and 24 months old. Our results suggest a specific distribution of α-TTP not only in the different layers of the hippocampus, but also a colocalization in certain INs populations. This suggest that the hippocampal INs could present a different susceptibility to redox imbalance according to their ability to use α-T as an external antio

PS5-31

Exercise-associated miRNA profile in miR-29a/b1 deficient mouse brain

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The microRNA-29 (miR-29) family is decreased in brain tissue in 30% of late-onset Alzheimer's disease (LOAD) patients, increasing the levels of their target mRNAs, such as BACE1 (implicated in the formation of the β-amyloid peptide). This family also shows a decrease in their circulating levels in both plasma and cerebrospinal fluid from LOAD subjects. However, whether this affects disease progression has not been studied yet. LOAD is associated with sedentarism, among other risk factors. Interestingly, results from our laboratory in murine models of both resistance and endurance exercises showed that plasma circulating levels of miR-29 family (c-miR-29), along with other c-miRs, and adult hippocampal neurogenesis (also affected in LOAD) are increased after long-term exercise intervention. To better understand how exercise-associated miRs can counteract the loss of miR-29 family, we took advantage of the previously described miR29a/b1 cluster knockout mouse model (miR-29 KO), which presents severe ataxia. Thus, in this study, we first explored maximal endurance and resistance performance in 16-week-old symptomatic miR-29 KO and their corresponding wildtype (WT; n=6/genotype). Then, we determined the expression of the found exercise-associated miRs in four brain areas: cortex, hippocampus, striatum, and cerebellum; along with mRNA levels of some proteins associated with AD and neurogenesis pathways, such as Bace1, Ranbp9, Dcx, Bdnf, Syt1, and Atg5. Our results showed that physical performance is impaired in miR-29 KO mice. Moreover, some brain exercise-associated miRs, along with their mRNA targets, are altered in specific brain areas regarding WT mice. Thus, the absence of miR29a/b1 cluster affects not only to physical fitness, but also modifies brain miR profile. Future studies will provide further information on whether exercise-modulated miRs can counteract the loss of this cluster in miR-29 KO mice after training. Translating these results to patients, knowing which exercise-associated miRs are beneficial for LOAD will allow to design therapies focused on modifying disease progression.

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PS5-32

PROJECTIONS OF THE RAT MEDIAL SUPERIOR OLIVE

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Sounds do not usually reach both ears at the same time. This difference in arrival time (interaural time difference [ITD]) is an extremely useful cue to localize the sources of low-frequency sounds in the horizontal plane. ITDs are encoded in the medial superior olive (MSO), one of the nuclei of the superior olivary complex. Although the rat is a favorite experimental model in auditory neuroscience, the projections of the rat MSO remain to be studied in detail with anterograde tracers. This may be due not only to the high-frequency hearing range of this species, which supposedly does not use ITDs for sound localization, but also to the extreme narrowness of its MSO, which renders experimental manipulations problematic.

To study the projections of the rat MSO, we have made small, single injections of the bidirectional tracer biotinylated dextran amine (BDA) into the MSO of this species and analyzed the trajectory, morphology and distribution of the labeled axons.

Our results are based on nine successful cases, whose injection site affected solely or almost exclusively the MSO. In all of them, dense plexuses of terminal axons were labeled ipsilaterally in the central portion of the dorsal nucleus of the lateral lemniscus and in the most dorsolateral portion of the central nucleus of the inferior colliculus, which are the regions of these nuclei where low-frequency sounds are processed. Minor projections, not previously described with anterograde tracers, were observed in the ipsilateral ventral nucleus of the lateral lemniscus and medial geniculate body of the thalamus.

Despite the widespread belief that the MSO of rats and mice is rather insignificant, our data demonstrate that it is hodologically similar to that of mammals with a lower auditory range, like the cat or the gerbil. They further suggest that MSO function is not limited to ITD coding.

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PS5-33

MORPHOLOGICALLY DISTINCT AFFERENCES TO THE LATERAL SUPERIOR OLIVE

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To locate sound sources, animals use interaural level differences (ILD), as sounds reach the nearest ear with higher intensity. ILDs are encoded in the lateral superior olive (LSO), a nucleus innervated by four neuronal types of auditory brainstem nuclei: spherical bushy cells (SBCs) and planar multipolar neurons of the ipsilateral ventral cochlear nucleus, principal neurons of the ipsilateral medial nucleus of the trapezoid body (MNTB), and small multipolar neurons of the contralateral ventral nucleus of the trapezoid body (cVNTB) (Gómez-Álvarez and Saldaña, 2016, J Comp Neurol 524:2230-2250). Neurons in the LSO are excited by sounds reaching the ipsilateral ear, and inhibited by sounds reaching the contralateral ear, yet how this integration occurs remains unclear.

We designed four tract-tracing experiments to label selectively each one of the projections to the rat LSO. We injected the tracer biotinylated dextran amine (BDA) into the anteroventral and dorsal cochlear nucleus (AVCoN and DCoN), superior paraolivary nucleus (SPON) and VNTB and studied the axons labeled in the LSO. All LSO afferents form flattened plexuses that follow the laminar organization of the LSO. These projections differ in morphological aspects, including the caliber and branching pattern of the axons, and the size and abundance of terminal and en passant boutons.

Injecting BDA into the DCoN, SPON, and VNTB labels selectively the axons of planar multipolar neurons, MNTB principal neurons, and cVNTB neurons, respectively. Conversely, injecting BDA into AVCoN to label the axons of SBCs leads to confusing results, since AVCoN is innervated by MNTB neurons that also innervate LSO. The axons of SBCs and MNTB principal neurons, which represent 80% of the neurons that innervate the LSO, have fewer synaptic boutons than those of planar multipolar neurons and VNTB neurons. Therefore, the functional relevance of the latter two projections should not be underestimated.

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PS5-34

Chronic full band recordings with graphene microtransistor neural interfaces for the discrimination of brain states

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Brain states (such as sleep, anesthesia or wakefulness) are characterized by specific patterns of cortical activity dynamics. Some of these patterns are observable in the infraslow frequencies of the spectrum (<0.1Hz) but are often missed due to the intrinsic limitations of the recording devices. We previously demonstrated that flexible arrays of graphene solution-gated field-effect transistors (gSGFETs) can record full-spectrum signal, including the infraslow component (DC, direct current-coupled), acutely in multiple sites of the rat brain. Here, we performed chronic implants of 16-channel gSGFET arrays on rat cerebral cortex and recorded full-band neuronal activity in order to test the long-term stability and biocompatibility of implanted devices, and to study the DC band during the transition between different brain states across different levels of anesthesia. We found that chronic epicortical gSGFET implants can record full-band signals with high stability, fidelity and spatiotemporal resolution for up to 6 months. Further, different brain states generated by different levels of anesthesia can be identified by the high pass filtered (AC, alternating current-coupled) spectrogram, which was complemented by the DC band for the quantification of the depth of anesthesia. We conclude that recording the infraslow activity by gSGFET interfaces provides an additional value for the identification of anesthesia levels and their associated brain states, and further supports the preclinical and clinical use of graphene neural interfaces for long-term multi-site minimally-invasive recordings of cortical activity.

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PS5-35

Distinct hemispherical responsiveness to transcranial static magnetic field stimulation?

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Transcranial static magnetic field stimulation (tSMS) is a non-invasive brain stimulation technique able to reduce corticospinal excitability when applied over the primary motor cortex (M1). Recently a few studies have been questioning this inhibitory effect of tSMS. Methodological differences between studies such as stimulating the right or left M1 might explain opposed findings.
Thus, we investigated whether tSMS over M1 does modulate corticospinal excitability, exploring whether tSMS modulates the right or left hemisphere differently. We recruited 40 right-handed healthy subjects (females: 22; mean age: 30.6±7.7 years). Separated into two same-sized groups, age and gender-matched, each subject underwent one tSMS session for 30 minutes applied either over right or left M1. We recorded 30 motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) from the first dorsal interosseous (FDI) muscle before and after (at 0, 15 and 30 minutes) tSMS intervention. The experiment was carried out with neuronavigation and threshold tracking methods to determine the individual resting motor threshold (RMT) and the stimulus output intensity to evoke a 1mV peak-to-peak MEP amplitude. Both measures were repeated after tSMS application.
The results show that 30 minutes tSMS produced a significant decrease in MEP amplitude at all time points (two-way repeated measures ANOVA, Dunnett, 0min, P=0.023; 15min, P=0.010; 30min, P=0.008), with no interaction between hemispheres (TIMExHEM: F3,114=1.16, P=0.328). However, when we analysed the hemispheres individually, we obtained a significant reduction of MEP amplitude for the right hemisphere (-21.5±28.9%; one-way repeated measures ANOVA, F3,57=4.36, P=0.008) with no significant differences for the left (-8.6±25.3%; one-way repeated measures ANOVA, F3,57=1.24, P=0.304).
Here we confirm the previously reported evidence that tSMS can modulate corticospinal excitability in an inhibitory sense for at least 30 minutes. Collectively, this effect is observed on both hemispheres. Nonetheless the results suggest a distinct responsiveness of hemispheres to tSMS, which could explain opposed findings between studies.

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PS5-36

Temporal binding of multisensory steady-state evoked responses

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Most events occurring in the external world concomitantly activate afferents from different sensory modalities. Building coherent representations of the environment requires integrating multisensory inputs. Some conditions such as autism spectrum disorder, schizophrenia, Parkinson's or Alzheimer disease exhibit sensory processing impairments and therefore, the perceptual experience of the world is altered.

Here we investigated the cortical and subcortical responses elicited by separated and concurrent auditory and visual inputs through steady state evoked potentials (SSEPs). Seven mice were implanted with electrodes in medial prefrontal cortex (mPFC), thalamic reticular nucleus (TRN) primary auditory (A1) and primary visual (V1) cortex and responses to only visual, only auditory and auditory-visual SSEPs at 10, 20, 40 and 80 Hz were obtained and analyzed through coherence and event-related estimates.

Across brain areas, concurrent and separated presentation of auditory and visual stimuli elicited evoked responses with different activation patterns across structures. Interestingly, the temporally congruent audiovisual condition elicited markedly enhanced auditory and visual SSEPs, that permeated to non-primary sensory areas (when compared to the only-visual or only-auditory SSEPs)

Taken together, these observations indicate that temporal congruency of audiovisual stimuli enhances the processing of multisensory inputs at sensory-specific stages of cortical processing, possibly through a dynamic binding of cortical and subcortical structures.

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PS5-37

M1- muscarinic control of slow oscillations and epileptiform discharges by light

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Different brain states are associated with specific patterns of cortical emergent activity. A highly synchronized activity pattern, slow oscillations, not only is associated to periods of deep sleep and anesthesia, but also to pathological conditions like non-responsive wakefulness syndrome and coma, and locally, to perilesional areas such as stroke. Neuromodulation techniques attempt to control neural activity, and their development is relevant for basic neuroscience and eventually, for the repair of disrupted functions in neurological disorders with altered activity patterns. A promising neuromodulation tool is photopharmacology, which is the control by light of drug activation, following chemical drug manipulation to be photoswitchable. Here, we investigated the effects of one of such novel drugs, BQCAAI (BAI), a photoswitchable type 1 muscarinic agonist obteined by the combination of benzyl quinolone carboxylic acid (allosteric part) with the muscarinic agonist Iperoxo (orthosteric part), to determine its effects over synchronized network activity - slow oscillations- in the cerebral cortex in vitro and in vivo. Our results show that slow wave activity was transformed into a faster oscillatory pattern in both preparations of the cerebral cortex following the illumination of the brain tissue containing BAI (1 micromolar BAI was used for in vitro and 5 micromolar BAI was used for in vivo experiments), demonstrating the effectivity of BAI. Higher BAI concentrations (> 10 micromolar) resulted in an epileptiform effect at in vitro. Interestingly, such epileptiform effect was not evoked by M2 muscarinic agonists (Barbero-Castillo et al, 2021, Advanced Science). Our results demonstrate that epileptiform effects of classical epilepsy models (pilocarpine) are indeed, M1-mediated, and sensitive to blockade by pirenzepine. These results shed light on the contribution of M1 acetylcholine receptor to cortical dynamics and validate the use of photoswitchable drugs for the spatiotemporal modulation of brain networks by light without requiring any genetic manipulation.

PS5-38

Phenotype Characterization of a Mice Model of Visual Blindness

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The presente work shows the phenotype characterization of a murine genetic model of absolute blindness. The animal model is based on the combination of a mutation in the Pde6brd10 gene, which results in a photoreceptor degeneration, together with a mutation in the Opn4 -/- gene, responsible of the melanopsin expresion in intrinsically photosensitive retinal ganglion cells.
The characterization of the visual functions of a double mutant Opn4 -/- x Pde6brd10 (OxRd) murine model has been carried out, applying a battery of behavioral tests, as well as in vivo electrophysiological recordings, which allowed us to know the degree of functionality of the retina and visual pathways. A structural characterization of the retina was also carried out using immunohistochemical labeling on retinal sections. The results were compared with wt mice and murine animal models that present both mutations separately. The OxRd animals showed a total suppression of all visual abilities. The different behavioral tests showed that characteristic physiological visual reflexes and visual behavior of these animals, such as the rejection of illuminated spaces or the pupillary reflex, were totally inhibited. A complete decrease in visual acuity was observed by the optomotor test, as well as the absolute disappearance of the various components of the waves of the full-field and pattern electroretinogram (ffERG, pERG), indicating the functional loss of the different cellular components of the retina. Likewise, no visual evoked potential (VEP) could be recorded in these animals. Immunohistochemical labeling support these data, showing a marked degeneration of the outer retinal layers, due to the of the Pde6brd10 mutation, as well as the absence of melanopsin labeling.
The combination of the mutations in the Opn4 -/- and Pde6brd10 genes has allowed us to generate an animal model that does not show any photosensitive element in its retina. This animal is unable to recognize light stimuli, which makes it a potential tool for the study of new therapeutic agents such as optosensitive agents.

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PS5-39

THE PROJECTION FROM THE INFERIOR COLLICULUS TO THE POSTERIOR INTRALAMINAR NUCLEUS OF THE THALAMUS STUDIED WITH ANTEROGRADE TRACERS

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The relationship between acoustic stimuli and emotions is very intriguing. The posterior intralaminar nucleus of the thalamus (PIN) acts as an interface between the auditory system and the limbic system: it receives information from neurons of the most superficial layer of the inferior colliculus (IC) and innervates the amygdaloid complex. Despite this pivotal role, the projection from the IC to the PIN remains to be studied in detail.

To characterize the projection from the IC to the PIN, we have injected the anterograde tracers Phaseolus vulgaris-leucoagglutinin (PHA-L), biotinylated dextran amine (BDA) and tetramethylrhodamine-conjugated dextran (D-TMR) into the superficial layers of the external cortex of the rat IC (ICx) and analyzed the trajectory, morphology and distribution of the axons labeled in the PIN. To delimit the PIN, we followed neurochemical criteria, because this nucleus is immunonegative for parvalbumin and immunopositive for calretinin and calbindin (Márquez-Legorreta et al., 2016, Front Neuroanat 10:82).

All three tracers provided congruent results, which showed that ICx axons run caudorostrally in the brachium of the IC and innervate diffusely the entire ipsilateral PIN identified neurochemically. Within the PIN, ICx terminal axons are thin and scarcely ramified, and bear small, homogeneous en passant and terminal synaptic boutons. Many labeled ICx axons extend rostromedially, past the PIN, to innervate the ipsilateral subparafascicular nucleus of the thalamus. Given the near absence of inhibitory neurons in the most superficial layer of the IC, the ICx-to-PIN projection is most likely excitatory.

The present results refine the delimitation of the PIN and will serve as a basis for future morphological and functional studies.

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PS5-40

Take care of your babies! Mouse pups produce pheromones that induce maternal behaviour.

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Maternal behaviour is a social behaviour characterized by conducts undertaken with the objective of increasing the survivability of the progeny. Female mice show several well-described behaviours when exposed to pups; however, they change depending on the stage the female is in, i.e. mother or virgin. We believe that the innate responses shown by mothers when exposed to pups, are triggered by a series of stimuli released by pups, specifically, we think that vomeronasal (VNO) related stimuli are essential for this kind of behaviours.

We have shown that pups activate the VNO in females compared with a non-social stimulus. Moreover, virgin and late-pregnant females show differential pup-induced activation of the vomeronasal amygdala, thus indicating hormone-induced changes in the response of females to pup chemosignals.

In our study, we aim to:

Find if pup-related volatiles are attractive for females (mothers and virgins), and explore if these have reinforcing properties over them.

Identify pup-derived volatiles that could act as pheromones triggering maternal behaviours.

First, we performed a conditioned place preference test, where females were exposed to anesthetized pups on one side and glass marbles on the other. Both stimuli were placed inside a stainless steel infuser so that females only had access to the volatiles released by pups. The results showed that while mothers found pup stimuli attractive and reinforcing, virgins did not. This suggests that pups produce volatile compounds acting as attractive pheromones for post-partum females.

Next, we extracted the volatolome (set of volatiles) of neonatal pups and youngsters at the age of weaning (week 4). Combining GC-MS with untargeted metabolomics we identified 10 volatiles present exclusively in the volatolome of neonatal pups. One of them, durene, has been shown to activate VNO neurons of adult mice. This and other identified compounds are good candidates for pup pheromones in mice.

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PS5-41

Human Brain oscillations and region distribution in two different fatiguing tasks

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Fatigue is one of the symptoms of many diseases such as multiple sclerosis, spinal cord injury and Parkinson's disease. It is a very disabling symptom that has a very significant detrimental impact on the quality of life of patients. The mechanisms underlying this symptom are not yet well understood. It is necessary to establish neurophysiological biomarkers and to know differs between patients and healthy people. Understanding these mechanisms could help optimize symptom treatments. The objective of this study is to describe how brain oscillations behave in two different fatiguing tasks and which brain regions are involved in the fatigue developed by the two different fatiguing tasks.
This study was carried out in healthy volunteers and was divided into two different experiments.
In Experiment 1, subjects participated in a rs-fMRI study after completing a fatiguing task inside RM. The participants were randomized to completed two different fatiguing tasks, an isometric task or a finger tapping task during two minutes. In Experiment 2, participants completed a crossover fatiguing-EEG study, with an isometric task and a finger tapping task during two minutes.
Results showed different brain regions involved in the two different tasks mechanisms of fatigue triggered by isometric contraction and repetitive movements. The consideration of these differences might help to optimize the study of fatigue in physiological conditions and neurological disorders.

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PS5-42

NAVIGATION TO A VIRTUAL PLATFORM TO EVALUATE ENCODING AND RETRIEVAL OF "EVERYDAY MEMORIES"

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The study of behaviour allows us to contextualize and provide biological meaning to experimentally acquired physiological and molecular data. Properly designed, behavioural tests represent a powerful tool for disambiguating neurophysiological processes that operate in parallel or sequentially. Encoding and retrieval of declarative memory are the two sides of the coin with respect to the neural mechanisms of learning [1]. Often, loss- and gain-of-function experiments to study the mechanisms underlying specific memory processes focus on misleading learning curves during manipulations, which likely reflect their effect on encoding, storage, consolidation, and/or retrieval, without discriminating relative contributions, nor identifying possible confounding factors due to performance alterations (i.e., attention and motor effects). Here we present a modification of the delayed-matching to place protocol of the water maze [2] to investigate "everyday memory" formation. The test is based on spatial navigation in a large arena and the finding of a virtual (invisible) "platform". Online video tracking of the animals is used to operate the maze, decreasing the light intensity in the room, and opening the access door to a home location when the animal crosses the target virtual platform location. The task requires remembering the location of the previous day platform and encoding the current location, to be tested on the next day. We show that, in a 3-day protocol with experimental interventions in the second day, this procedure allows dissociation between memory encoding, retrieval and consolidation, measured in the behavioural performance. Furthermore, the same animals can be tested repeatedly, increasing the statistical power in a longitudinal design. The implementation in a dry maze, facilitates concomitant electrophysiological recordings and brain network manipulations based on deep brain electric or optogenetic stimulation.

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PS5-43

Intraneuronal β-amyloid but not Tau Accumulation Enhances Fear and Anxiety in Alzheimer's Disease Transgenic Mice

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Progressive cognitive decline and neuropsychiatric symptoms are common clinical features of Alzheimer's disease (AD). Emotional disturbances, including anxiety and fear, occur very early during clinical AD, when individuals meet criteria for mild cognitive impairment. The mechanistic link between the classical cerebral disease pathological features, amyloid-β (Aβ) and tau, and amygdala-dependent emotional symptoms in AD is largely unclear. Here we show that anxiety and fear symptoms are associated with Aβ accumulation but not tau pathology in emotion-related brain regions of AD transgenic (Tg) mice. By generating and analyzing littermate control, APP, Tau and APP/Tau Tg mice we demonstrate an age-dependent increase of Aβ and phospho-tau accumulation in the hippocampus and basolateral amygdala (BLA) of APP/Tau Tg mice. Both males and females APP and APP/Tau Tg mice, but not Tau Tg mice, displayed enhanced innate and conditioned fear symptoms and a deficiency in extinction fear memory consolidation coinciding with enhanced accumulation of Aβ in β-aminobutyric acid (GABA)ergic neurons of the BLA. This behavioral alterations occur in parallel with decreased activity of hippocampal neurons as assayed in APP/Tau; cfosp-EGFP reporter mice. Overall, these results suggest a novel pathogenic role of intraneuronal Aβ in GABAergic interneurons on anxiety and fear symptoms in AD. This study clarifies the relationship between amyloid and tau pathologies, and it provides a useful mouse model to delineate the neurobiological and pathological mechanisms underlying neuropsychiatric symptoms in AD.

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PS5-44

Immune receptor TLR4 mediates cognitive deficit induced by high sodium diet

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It has been recently proposed that high sodium diet (HSD) triggers an immune response in the gut, characterized by an expansion of Th17 lymphocytes and increased IL-17 levels, which suppresses resting cerebral blood flow, leading to cognitive impairment (Faraco et al. 2018). Several studies have highlighted the importance of adult neurogenesis and hippocampal neuroinflammation in the development of dementia (Hort et al. 2019, Moreno-Jimenez et al. 2019). However, these processes have not been studied in the context of HSD. Here, we hypothesize that the immune receptor TLR4, due to its participation in both neurogenesis and immune response, could be involved in the development of cognitive impairment associated with HSD.

For investigating this, eight-week-old male wild type C57Bl/6 (WT) and TLR4-deficient B6.B10ScN-Tlr4lps-del/JthJ (TLR4-/-) mice were fed either a normal diet (ND, 0.4% NaCl) or a high sodium diet (HSD, 4% NaCl). Hippocampus-dependent memory deficits were evaluated after 5 weeks of diet using the Contextual Fear Conditioning test (CFC). Neurogenesis and neuroinflammation were evaluated by immunohistochemical studies and cytokine levels were assessed in brain and plasma.

Our data demonstrate that, in WT mice, HSD-induced memory deficits in the CFC shown by a lower freezing response compared to those mice fed with ND. On the contrary, this deficit was not present in TLR4-/- HSD animals. In addition, HSD in WT mice also promoted a reduction in hippocampal neurogenesis (demonstrated by the quantification of doublecortin+ cells), which positively correlated with cognitive impairment. Finally, WT HSD animals showed an increase in plasma levels of IL-17A, which was not observed in TLR4-/- HSD animals.

In conclusion, HSD in rodents produces a peripheral immune response characterized by increased IL-17A levels, which promotes a decrease in hippocampal neurogenesis and cognitive deficits in hippocampus-dependent memory. This immune response is not present in TLR4-/- animals, suggesting that TLR4 plays a crucial role in the development of cognitive impairment associated to HSD-induced IL17-dependent pathways in this model.

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PS5-45

Global hypoperfusion model of bilateral common carotid artery stenosis induces hippocampus-dependent memory deficits

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Chronic cerebral hypoperfusion due to carotid artery stenosis is one of the main causes of vascular cognitive impairment (VCI), the second cause of dementia behind Alzheimer's disease (AD; Iadecola 2013). Bilateral common carotid artery stenosis (BCCAs) in rodents is a well-established model of cerebral hypoperfusion in which most studies have focused on white matter pathology and subsequent cognitive deficit. Several reports have recently highlighted the importance of adult neurogenesis and neuroinflammation in the development of dementia (Hort et al. 2019, Moreno-Jimenez et al. 2019). However, so far, the implication of these processes in the BCCAS model and its relationship with cognitive hippocampal deficits have not been addressed.

To that aim, mice were subjected to global cerebral hypoperfusion by using the BCCAS procedure, and hippocampal memory and neurogenesis were assessed after 3 months. Cognitive function was evaluated using the Novel Object Location test (NOL). Hippocampal neurogenesis and neuroinflammation were evaluated by immunohistochemical methods, and cerebral cytokine expression was measured by RT-qPCR. Hypoperfusion was assessed by arterial spin labelling-MRI.

Our data demonstrate that hypoperfused mice displayed hippocampus-dependent memory deficit demonstrated by a lower recognition index in the NOL than sham control animals. Along with the cognitive deficit, neurogenesis assessed by the number of doublecortin-positive cells showed a significant decrease in BCCAS-mice and their analysis also suggest an altered morphology. Finally, our results also showed that hypoperfusion promotes a reduction in microglia branches.

Therefore, we can conclude that the hypoperfusion originated by BCCAS mouse model in brain lead to cognitive deficit concomitant to impaired hippocampal neurogenesis and morphological alterations in the microglia.

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PS5-47

Microglia Regulate Learning and Memory through NF-κB

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Microglia, the resident immune cells of the CNS, have been implicated in brain plasticity and function. However, the mechanisms remain largely unknown. Here, we show that Cre-dependent removal of the RelA subunit of the NF-κB transcription factor from adult microglia results in impaired learning and long-term potentiation. Depletion of RelA elicits changes in chromatin accessibility and transcriptome landscapes of microglia associated with specific gene regulatory programs driving the activation of specific microglia phenotypes. Our findings suggest that NF-κB gene products drive specific microglia phenotypes modulating neuronal circuits for learning and memory.

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PS5-48

LEARNING CONDITIONS INFLUENCE HIPPOCAMPAL-DEPENDENT MEMORY AND CONTEXT DISCRIMINATION

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In contextual fear conditioning (CFC), learning occurs when an aversive foot-shock (unconditioned stimulus, US) is presented within a context (conditioned stimulus). Hippocampal circuits, in particular CA1 and dentate gyrus (DG), integrate sensory and spatial information and contribute to the formation of the associative memory. Learning is expressed in the form of a conditioned response (CR, freezing), which can be restricted to the conditioning context (discrimination) or extended to a similar neutral context (generalization). Although mice discriminate contexts efficiently, they show a wide range of CR persistence in both conditioning and neutral contexts. The objectives of this work are: 1) To identify behavioural traits and learning conditions that influence this variable discrimination capacity and 2) to elucidate the impact of those behavioural traits and learning conditions on the activity of CA1 and DG neurons using fibre photometry.

We first analysed several behavioural traits (locomotion, centre/periphery exploration, shock reactivity, freezing) throughout the CFC training and test sessions. Correlation analysis showed multiple significant associations of behavioural traits with discrimination suggesting that individual variation in natural behaviours may predict discrimination capacity. Regarding learning conditions, we found a significant correlation between the position within the cage (centre or periphery) where mice received the US and discrimination. Based on this, we designed an experiment to control shock reception zone. This manipulation resulted in differences in mice discrimination, suggesting that learning conditions influence context discrimination. Fibre photometry revealed that locomotion, US and freezing differentially modulate the activity of CA1 and DG. Importantly, we observed different levels of neuronal activity depending on the cage position (centre/periphery) occupied by mice.

In conclusion, our results show that discrimination capacity relies on learning conditions that affect the hippocampal circuits responsible for memory encoding. This suggests that learning conditions regulate discrimination through modulation of neural networks involved in associative learning.

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White matter hyperintensities and cognitive reserve affect working memory status and trajectory: A task-based functional Magnetic Resonance Imaging study

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Cognitive reserve (CR) theory hypothesizes that some lifestyles such as years of formal education may modulate the relationship between cognition and age-related brain changes. The aim of this study was to characterize the longitudinal (2-year follow-up) functional magnetic resonance imaging (fMRI) changes and cognitive trajectories among healthy older participants stratified at baseline according to their education level (as a proxy of CR) and the degree of white matter hyperintensities (WMHs) exhibited (i.e., degree of atrophy). Eighty-six participants (aged: 63-75 years at baseline) were included. At the two time-points, we acquired MRI data in a 3T Siemens scanner: T1-weighted 3D MPRAGE, FLAIR and fMRI-EPI scans during an N-back task. FLAIR images were used to compute the WMH volume using LST toolbox from SPM and fMRI scans were analyzed using FEAT-FSL software, statistical significance was set at $p<0.05$ and $z>2.3$ (cluster wise corrected). We found that education contributed positively to a higher cognitive level in the intercept, rather than modulate the slope. However, WMH burden mediated the relationship between CR and cognition. Among the high educated participants, those with high WMHs seemed to resist the increase in WMH volumes through the over-activation of task-related areas and the recruitment of additional brain regions. In contrast, those participants with low WMH showed a young-like activation pattern and cognitive stability. Regarding the low educated participants, the increase in WMHs induced a decrease in cognitive performance, and the fMRI analyses suggested an unsuccessful attempt of compensation through the recruitment of non-task-related areas.

Our findings demonstrate that education is related to a better cognitive progression in cognitively normal older adults, but it does not predict cognitive trajectory on its own since WMHs load has an impact on brain activation, resulting in distinct cognitive profiles.

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PS5-50

Behavioural characterization of motor and cognitive everyday life habits in Parkinson's disease

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Humans can simultaneously and easily shift between automatic/habitual to voluntary/goal-directed modes of behavioural control. Habits (stimulus-response) allows us to perform well-practiced tasks with minimal or no conscious effort. In Parkinson disease (PD), there is a differential loss of dopamine (DA) along the caudal sensorimotor putamen initially transferring to more rostral regions as the disease progresses. The sensoriomotor putamen is primarily implicated in habitual control of behaviour therefore possibly explaining some motor deficits in PD such as arm swinging, walking and writing.

Our aim was to investigate with a more ecological approach whether early dopaminergic cell loss in PD (a) alters everyday life motor habits and (b) if as well cognitive everyday life habits are impaired in PD compared to controls.

We measured habitual behaviour in 36 early PD patients and 44 HC during performance of a natural habitual motor (handwriting, one of the most well-learned and automatic tasks) and cognitive tasks (PD = 14; HC = 14) (Go/noGo Associations Tasks GNAT on implicit bias). Tasks were developed to differentiate between habitual and goal directed components. In the writing task, we collected data from the most automatic (e.g. signature, Spanish) to more goal-directed conditions (e.g. Polish, Greek). In the GNAT, we used four kind of stimuli to create four possible Go conditions: two congruent and two incongruent associated to familiar and unfamiliar associations.

In the natural habitual motor task (handwriting), PD patients showed reduced automatism in the execution of habitual conditions (Spanish and signature writing) compared to controls. However, in the cognitive habitual task, results reveal similar habitual responses in both groups, showing faster responses for congruent conditions than incongruent ones.

Our results suggest larger differences in the motor domain of everyday life habits whereas the cognitive one remains unaffected in early PD, indicative of specific deficient use of motor habits.

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PS5-51

Subjective cognitive complaints are related to cognitive dispersion and resting-state networks segregation in a middle-aged healthy population

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Cognitive dispersion index (DI) is defined as individual variability in performance across cognitive tests, which has been proposed as an independent predictor of cognitive decline and it has been associated with alterations in brain functional integrity. Our aim was to study the interactions between DI and cognitive complaints defining their cerebral functional correlates using System Segregation (SyS), a graph metric that quantifies how resting-state networks are segregated from each other.

A total of 619 healthy volunteers (age range: 45-66 years; 301 female) from the Barcelona Brain Health Initiative (https://bbhi.cat/en/) cohort with available neuropsychological assessment and functional Magnetic Resonance Imaging (fMRI) acquisitions were included in our analyses. The sample was stratified into high (N=285) and low (N=333) cognitive complaints reported by Neuro-QoL. Then, we computed DI for episodic memory (EM-DI), executive functions (EXE-DI) and speed of processing (SP-DI), as well as for global cognition (C-DI). Individual SyS was estimated based on Schaefer fMRI atlas resting-state networks. All the analyses were adjusted by age, gender, and years of education.

Those subjects with low cognitive complaints exhibited higher performance than those with high complaints regarding SP (t=3.455, p=0.001), EXE (t=2.785, p=0.006) and global cognition (t=2.724, p=0.007). However, there were no group differences for DI measures, neither for SyS. Taking into account each group independently, those subjects with high cognitive complaints evidenced negative correlations between almost all DI measures and the corresponding performance (EM-DI and EM: r=-0.131, p=0.027; EXE-DI and EXE: r=-0.136, p=0.022; C-DI and global cognition: r=-0.148, p=0.013). Interestingly, SP was associated with lower EM-ID performance (r=-0.158, p=0.008) and higher SyS (r=0.154, p=0.017). No significant correlations were identified for the low-complains group.

Segregation of the brain's connectome into distinct functional networks was associated with speed of processing among subjects with higher rates of cognitive complaints.

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PS5-52

Long-term turnover dynamics in area CA1 of hippocampus are consistent with plasticity of non-spatial inputs

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Recent chronic imaging experiments in mice have revealed that the hippocampal code exhibits non-trivial turnover dynamics over long time scales [1]. Specifically, the subset of cells which are active on any given session in a familiar environment changes over the course of days and weeks. While some cells transition into or out of the code after a few sessions, others are stable over the entire experiment. The mechanisms underlying this turnover are unknown. Here we show that the statistics of turnover are consistent with a model in which non-spatial inputs to CA1 pyramidal cells readily undergo plasticity, while spatially tuned inputs are largely stable over time. The heterogeneity in stability across the cell assembly, as well as the decrease in correlation of the population vector of activity over time, are both quantitatively fit by a simple toy model with Gaussian input statistics. In fact, such input statistics emerge naturally in a network of spiking neurons operating in the fluctuation-driven regime. This correspondence allowed us to map the parameters of a large-scale spiking network model of CA1 onto the simple statistical model, and thereby fit the experimental data [2] quantitatively.
Our model suggests that the internal representation of space in the hippocampus evolves over time mainly due to changes in non-spatial inputs, which may represent changing contextual cues, or simply the passing of time. It also suggests that the locus of plasticity underlying turnover may be in the inputs from the entorhinal cortex, and not necessarily CA3.

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[2] Rubin, Alon, et al. "Hippocampal ensemble dynamics timestamp events in long-term memory." Elife 4 (2015): e12247.

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PS5-53

Neural network dynamics underlying the adjustment of temporal evidence weighting in perceptual decisions

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During perceptual decision making, sensory information can be accumulated using distinct strategies; weighting some stimulus epochs more heavily than others. A recent study has shown that primates can flexibly adapt their temporal weighting strategy to the stimulus statistics (Levi et al., Eneuro 2018). Sensory stimuli with more information at the beginning of the trial produced early weighting, while stronger sensory evidence in later stimulus epochs caused a switch to a late weighting strategy.

To shed light on how this flexible adjustment can be mechanistically implemented at a neuronal level, we used a two-area firing rate model composed of a sensory and a decision circuit with bottom-up and top-down connectivity (Wimmer et al., Nat. Commun. 2015). We included a time-varying modulation signal, ("choice commitment" signal), that altered the attractor dynamics of the decision circuit. This modulation signal affected the decision circuit in two ways. Firstly, it initiated the decision process by pushing the network into a competition regime. Secondly, it changed the decision dynamics by accelerating or delaying the choice, similar to an urgency signal.

The model could reproduce the experimentally observed primacy weighting for early and flat stimulus statistics and late weighting for late stimulus conditions when the time-course of the modulation signal reflected the stimulus statistics. We reasoned that the modulation signal may be related to the subject's task engagement, which we measured as the time needed to execute a successful fixation at the start of the trial. Consistent with the model, we found that the subject's engagement was higher (faster fixation) in the early weighting condition and lower (slower fixation) for the late condition.

Preliminary analysis of neural data recorded from areas MT and LIP indicated that the neurons' pre-stimulus activity was correlated with task engagement, providing further evidence for the modulation signal.

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PS5-54

Control limitations shape perceptual decision making

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Adaptive behavior in a perceptual decision making (PDM) task involves a trade-off between the performance deficit of responding too soon and the cost of time associated to gathering evidence. The optimal solution to this problem has been understood using the Partially Observable Markov Decision Process framework (POMDP). However, these kinds of policies assume perfectly rational agents and therefore ignore constraints that real agents have to confront. Here, we generalize ideas from optimal control theory to derive optimal policies that solve a categorical PDM task in the presence of a "cost of control", which penalizes policies that deviate from the agent's default actions.
In particular, we consider the effect of impulsivity, a spontaneous tendency to respond (consistent with the concept of exploration).

We provide semi-analytical solutions for the probability that the agent will choose an option at a given time with a given belief, deriving predictions on measurable observables: choice, reaction time (RT) and decision confidence. We show that when the cost of control is significant, the behavior of decision confidence departs from the POMDP solution and resembles predictions of signal detection theory. Moreover, this regime also provides a natural account of "lapses" dictated by the default dynamics, as opposed to the standard descriptions that rely on an ad-hoc independent guessing process. Finally, we showcase the model's ability to generate history effects through a biased default policy, which can be modulated through the cost of control and contrasts with the effects generated by reward asymmetries or typical history-dependent heuristics.

Overall, our results clarify the link between the observed phenomenology of decision confidence and different notions of optimality, and also provide a more general notion of normative behavior that includes both task contingencies as well as unavoidable costs faced by real organisms.

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PS5-55

AhR Deletion Reduces Amyloid Plaque Accumulation and Axonal Dystrophy in the APP KI NL-F Alzheimer's Mouse Model

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An interaction between intrinsic and environmental factors probably contributes to the molecular processes that drive Alzheimer Disease (AD). Although variation in specific genes increases the risk of AD, one of the main risk factors is age. However, how molecular processes of aging predispose to, or become deregulated in AD, still remains to be understood. Studies in different organisms from invertebrates to humans show that the Aryl Hydrocarbon Receptor (AhR), that integrates environmental stimuli (from pollutant to diet components with agonist properties) into transcriptional changes, is implicated in the aging process and therefore, we decided to investigate its role in age-associated neurodegeneration.

To that aim, we crossed the APPNLF knock-in mouse model of AD with an AhR knockout mouse (AHR-/-). Histological characterization of plaque development, soluble and insoluble Aβ loading, and tandem mass tagging (TMT)-based quantitative proteomics analysis of cortex samples were carried out for investigating the potential role of AhR in AD development.

Our results demonstrate that the absence of AhR reduces amyloid plaque formation, Aβ load and plaque-associated dystrophic neurites. Importantly, correlation network analysis and functional enrichment from proteomic data identified a set of pathways associated with mitochondrial metabolism, neuron projection and synaptic vesicles among others.

Therefore, we can conclude that AhR plays a pivotal role in the development and progression of AD and suggests that the AhR pathway and/or its modulation by exogenous or endogenous agonists can be explored for AD therapy.

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PS5-56

Impact of tauopathies on the functional organization of neuronal cultures

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Tau protein aggregates are a key element in the development of certain neurodegenerative diseases, defined as tauopathies. This type of diseases includes relevant pathologies such as Alzheimer's Disease (AD) which affects more than 47 million people worldwide [1]. When Tau becomes pathological it might induce neurodegeneration through different mechanisms [2], causing a disruption of synaptic communication and, therefore, changing the functional organization of the neuronal circuit. Due to sheer size of the brain, and the difficulty to monitor tauopathies at a cellular scale, an interesting approach is to use in vitro neuronal circuits derived from mouse brain. Here we use such idea to understand tau-induced functional alterations in vitro and to develop strategies to block tau action and protect the neuronal circuits.

To prepare the neuronal cultures, cortical mouse embryos tissue is mechanically dissociated and planted in glass covers. Cells are infected with an adeno-associated virus, GCamp-6, a calcium marker, at day in vitro 1 (DIV 1) and treated with Tau and different control conditions every time the medium is changed. Spontaneous activity is registered every from DIV 7 to DIV 16 with the help of a fluorescence microscope attached to a hight-speed camera. Data then is analysed applying MATLAB routines developed in Soriano's Lab.

We found that the tau-treated, pathological neuronal cultures exhibit a tendency towards an excessive synchronization, which we associate to the damage or loss of activity-regulatory mechanisms in the neuronal networks.

The project leading to these results has received funding from "la Caixa" Foundation (ID 100010434) under the agreement LCF/PR/HR19/52160007. Its main objective is to determine the molecular mechanism involved in different tauopathies, characterise the spread of Tau in neuronal circuits and develop possible selective treatments that slow or prevent the spread of Tau molecular aggregates.

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PS5-57

Neural migration is impaired in the APP/PS1 Alzheimer's mice model due to increase senescence in migrating precursors cells

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Adult neurogenesis occurs in two neurogenic niches: the ventricular-subventricular zone (V-SVZ) and subgranular zone (SGZ). The V-SVZ is composed by a heterogeneous cellular population: neural stem cells (B cells), intermediate progenitors (C cells), young migrating neurons (A cells), ependymal cells and mature astrocytes. V-SVZ zone can generate new neurons, oligodendrocytes, and astrocytes, which migrate to an adequate position. New neurons mainly migrate to olfactory bulbs (OB) throughout the rostral migratory stream (RMS). In Alzheimer's disease, both olfactory loss and neurogenesis impairment have been described at a very early state.

We aimed to investigate neurogenesis and neuronal migration in the V-SVZ in a murine model of Alzheimer's disease, the APP/PS1 mice model. We measured the levels of proteins involved in senescence (β-gal), apoptosis (Smac-DIABLO), neural progenitors (DCX and PSA-NCAM) and mature neurons (NeuN) and in some cases, we determine their co-localization by immunofluorescence technique and we obtained microscopy images from the V-SVZ, RMS and OB; also we use flow cytometry for cell cycle characterization.

Our results showed that migrating precursors neurons were accumulated in the V-SVZ in the APP/PS1 mice model. Furthermore, we found an increase of cells in the G1 phase and a decrease in the S phase in V-SVZ from APP/PS1 mice. We observed that the accumulated migrating cells were in a senescence state, while an important proportion of astrocytes suffered apoptosis in the V-SVZ of the APP/PS1 mice. Finally, we determined that in the RMS from APP/PS1 mice there were fewer migrating neurons than in WT; and in the olfactory bulb of APP/PS1 mature neurons decreased. These results indicate a failure in the neural migration. To sum up, we conclude that neural migration is impaired in a mice model of Alzheimer's disease probably contributing to the early symptoms of the disease.

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PS5-58

Oxidative damage in middle-aged apolipoprotein E4 carriers

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Apolipoprotein E4 (APOE4) is the main genetic risk factor for many diseases, including Alzheimer's disease (AD). However, while oxidative stress is a characteristic of AD pathology, our previous study found that young healthy APOE4 carriers present reductive stress. As AD pathology starts years before the onset of clinical symptoms, it is possible that the oxidative status of APOE4 carriers might change as they reach middle age. Therefore, we conducted a prospective study with the objective of analyzing the oxidative status of the same APOE4 carriers, after a 10-year interval. We recruited 39 cognitively healthy adults that participated in the previous study, 24 APOE4 carriers (14 heterozygous and 10 homozygous) and 15 non-carriers. Subjects had a mean age of 52 years (range 35-64 years) and 61% were women. Blood samples were collected from all subjects and levels of plasma malondialdehyde (MDA) and whole blood glutathione were measured by high performance liquid chromatography and spectrophotometry, respectively. Levels of oxidized (GSSG) and reduced glutathione were used to calculate oxidized/reduced ratio. Current results showed that, although there were no differences in glutathione levels, APOE4 carriers presented significantly higher levels of MDA when compared to non-carriers. Furthermore, APOE4 carriers presented a significant increase in GSSG, oxidized/reduced ratio, and MDA levels through time, which did not occur in non-carriers. Although age affected MDA levels in APOE4 carriers, with a higher increment in those subjects older than 50 years, gender and genotype had no effect on either blood parameter. We concluded that the oxidative status of the cognitively healthy, middle-aged APOE4 carriers in our study changed through time, with a reversal of the previous reductive stress and current higher markers of oxidative damage.

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PS5-59

Use of fluorophore-conjugated peptides to asses putative targeting to glia of peptide-drug hybrid molecules as a new therapeutic approach for Multiple Sclerosis.

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Demyelinating diseases such as Multiple Sclerosis (MS) are a collection of pathologies that involve the degradation of the myelin sheath of the neurons, resulting in severe handicaps for neurological physiology. Oligodendrocyte precursor cells (OPCs) are the cells that upon differentiation and maturation (re)generate the myelin necessary for the correct function in central nervous system (CNS). Thus, finding pharmacological approaches to stimulate OPCs maturation into myelinating oligodendrocytes (OLs) is considered one the of the great challenges in MS treatment. Previous work from our group has shown the effect of compounds that enhance this (re)myelinating process [1].

However, one of the additional key challenges on systemically administered drugs is finding strategies to deliver them into their specific target organs or cells. In this sense, small peptides have previously exhibited promising features as target-specific interactors [2], thus becoming interesting putative carriers in hybrid molecule (carrier-drug) treatment strategies.

In this work, we utilized ad hoc designed small peptides, CTB2.20 and CTB 2.21 labelled withfluorophore Cy3 to validate the specificity of those peptides delivering small molecules into OPCs, both in vivo and in different cell cultures.

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PS5-60

Male sex bias in Parkinson's disease is linked to an accelerated age-dependent neuromelanin accumulation

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Men have a higher incidence and prevalence of Parkinson's disease (PD), earlier disease onset, more severe motor symptoms and progression, and more frequent cognitive decline compared to women. However, most PD studies do not consider the influence of sex, thus the molecular mechanisms underlying sex differences in PD remain unknown. Sex steroids modulate dopaminergic pathways, in both normal and pathological states, and estrogens improve PD symptoms in both men and women. Estrogens are also able to modulate melanin production in the skin and we have recently reported, in both humans and experimental animals, that excessive age-dependent intracellular neuromelanin accumulation above a pathogenic threshold triggers PD pathology. Here we assessed whether differences in neuromelanin production/accumulation could underlie the differential effect of sex on PD. First, using postmortem human brain tissue, we found that intracellular neuromelanin levels within nigral dopaminergic neurons from age-matched control subjects are significantly higher in men than in women and that men reach earlier the pathogenic threshold of neuromelanin accumulation, even in absence of overt PD. We then assessed the effect of sex on the only rodent model currently available of age-dependent neuromelanin production within PD-vulnerable neurons, based on the viral vector-mediated expression of melanin-producing enzyme tyrosinase (AAV-hTyr) in the substantia nigra of rats. This model, developed by our group, exhibits major PD features in parallel to progressive neuromelanin accumulation. We observed that AAV-hTyr-injected male rats exhibit an earlier and greater accumulation of neuromelanin compared to female animals, reaching earlier the pathogenic threshold of intracellular neuromelanin accumulation. Remarkably, ovariectomized (OVX) female rats injected with AAV-hTyr accumulated neuromelanin more rapidly than non-OVX female animals and ultimately reached pathological neuromelanin levels similar to their male counterparts. These results suggest that an increased/accelerated accumulation of neuromelanin in men across life may underlie their higher risk to develop PD, compared to women.

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PS5-61

MALDI Imaging in mice brains reveals novel peptides signatures associated to the progression of Alzheimer`s disease that can be reversed by ubiquinol

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Oxidative stress (OS) is a prodromal signature associated to the debut and progression of Alzheimer's disease (AD). OS is often described as a self-propagating phenomenon caused by an imbalance between oxidant and antioxidant systems, namely an overproduction of reactive oxygen species (ROS), which overwhelms the intrinsic antioxidant defenses. In AD, there is a growing evidence supporting the link between ROS-mediated damage and mitochondrial dysfunction, with endoplasmic reticulum (ER) stress and proteostasis imbalance. Our previous work demonstrated the protective role of ubiquinol (Ubi), the reduced form of coenzyme Q10 (CoQ10), in the 3xTg-AD mice model of AD, preventing hypoxia and amyloid-β (Aβ) peptide deposition in hippocampal and neocortical areas at onset (6 months) and advanced (12 months) stages of disease in animals fed with Ubi-supplemented diets from premorbid (2 months) ages. Using a similar approach, 2-month-old wild-type and 3xTg-AD mice were fed with standard or Ubi-supplemented diet, up to 6- and 12-month. After performing behavioural tests, animals were perfused, brains were included in paraffin and sections were analyzed and visualized by MALDI Imaging. Proteins inferred from significantly altered m/z peaks were analyzed and clustered with MEV4 and Metaboanalyst 5.0, followed by FunRich and STRING. Results were validated by immunofluorescence and confocal microscopy in hippocampal and cortical areas. Behavioral tests showed an Ubi-dependent rescue in the AD-associated cognitive decline. MALDI-Imaging analysis revealed age-dependent differential peptide signatures in the 3xTg-AD model vs. wt mice in hippocampal and cortical areas, being altered those related to protein translation, ROS production and ER stress, among others. Our results indicate that Ubi-supplemented diets could delay AD progression in the 3xTg-AD model by reducing OS and maintaining the proteostasis balance.

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PS5-62

Alpha-synuclein interacts with neuromelanin to enhance Lewy body formation and neurodegeneration in neuromelanin-producing parkinsonian rodents.

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Parkinson's disease (PD) is characterized by a preferential loss of neurons that contain the pigment neuromelanin, especially dopaminergic neurons of the substantia nigra (SN), and the presence in affected neurons of alpha-synuclein (aSyn)-containing insoluble cytoplasmic aggregates termed Lewy bodies (LB). While aSyn aggregation is considered a central pathogenic event in PD, the mechanisms and significance of LB formation remains unknown. In PD brains, LBs appear in close physical association with neuromelanin within affected neurons. In addition, it has been reported that aSyn redistributes to the lipid component of neuromelanin at early PD stages and that aSyn is entrapped within neuromelanin granules extracted from PD, but not control, brains. The increased concentration of neuronal aSyn and neuromelanin pigment in SN neurons may predispose these neurons to LB formation and cell death. However, it has not been possible yet to experimentally assess in vivo a potential pathological interaction between aSyn and neuromelanin because, in contrast to humans, neuromelanin is absent in common experimental animals such as rodents. We recently developed the first rodent model of human-like neuromelanin production based on the viral vector-mediated nigral expression of melanin-producing enzyme tyrosinase (AAV-hTyr). This has revealed that neuromelanin can trigger PD pathology when accumulated above a specific pathogenic threshold. Here we assessed the potential interaction between aSyn and neuromelanin by combining aSyn overexpression with hTyr-induced neuromelanin production in rodents. Compared to regular non-melanized animals, AAV-mediated nigral expression of human aSyn in melanized hTyr-expressing rodents resulted in an increased formation of aSyn oligomeric species within melanized neurons, as assessed by proximity ligation assay (PLA), an enhanced and continuous production LB-like inclusions and an aggravated nigrostriatal denervation. Our results indicate that increased levels of aSyn, as it occurs in PD patients, may accelerate and enhance neuromelanin-linked PD pathology.

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PS5-63

TRAUMATIC BRAIN INJURY INDUCES A BIPHASIC LONG-TERM EFFECT ON ADULT HIPPOCAMPAL NEUROGENESIS

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Several important cognitive functions affected by traumatic brain injury (TBI) depend on the hippocampus, which harnesses several forms of neural plasticity, among them adult neurogenesis, the generation of new neurons throughout life. Adult hippocampal neurogenesis is a process involved in memory, learning and control of anxiety, cognitive functions which result impaired after TBI. We hypothesize that TBI induces fast and long-term changes in both neural stem cells (NSCs) and newborn neurons which could subsequently alter hippocampal and brain functioning. Using a model of controlled cortical impact (CCI) we have found that TBI has a dual effect on neurogenesis: In the short term (up to two months) it causes an increase in the number of newborn neurons but with aberrant migration, increased soma size and altered electrophysiological properties; in the long term, neurogenesis results impaired by a reduction in the number of immature neurons. We also suggest that the alteration in the expression of Rho Family GTPase 2 (Rnd2) could be causing some of the morphological changes in the immature neurons as well as their aberrant migration and thus could be a target to prevent TBI-induced aberrant neurogenesis, a hypothesis that we are currently investigating at the cellular level. In addition, we have found that NSCs get activated in higher numbers early after TBI, a result that could explain the later reduction in neurogenesis.

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PS5-64

Sex differences in the kynurenine pathway in a mouse model of neuropathic pain and depression comorbidity

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Pain and depression are frequently comorbid disorders and both are more prevalent in women than men. The neurobiological mechanisms underlying this comorbid situation are still unknown and poorly investigated according to the sex. Kynurenine metabolism is hypothesized to be a pathway linking pain and depression, in part, by the role of the kynurenine in the central nervous system.

Hence, we propose that neuropathic pain could alter the kynurenine pathways promoting the onset of anxiety and/or depressive-like behaviors. Thus, sensorial and depressive-like behaviors, as well as plasma and central levels of tryptophan and kynurenine in a mice model of neuropathic pain (chronic constriction injury, CCI) were evaluated by using ELISA technique at short (ST) and long-term (LT) after nerve injury in both sexes.

Basal kynurenine plasma levels were significantly higher in females than in males. Nerve injured animals, CCI-ST and CCI-LT, showed higher levels of kynurenine in the prefrontal cortex (PFC). This increase was specially relevant in the CCI-LT group and it temporally coincide with the onset of the depressive-like phenotype showed by an increase of the immobility time in the forced swimming test. Interestingly, kynurenine enhancement was significantly higher in the PFC of females in comparison with male mice.

These data suggest that kynurenine is an important mediator in the comorbid chronic pain-depression situation and could be involved in the different sex-vulnerability observed in both pathologies.

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PS5-65

KINETIC AND DISTRIBUTION OF NANOEMULSIFIED ALPHA-TOCOPHEROL IN AGEING MOUSE MODELS

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Vitamins, especially the alpha-tocopherol (αT) isoform of vitamin E (VitE), have been widely studied as an anti-ageing agent due to its well-known antioxidant properties. αT is highly sensitive to the action of external agents and its action is reduced by the presence of biological barriers, moreover it shows an erratic and irregular oral absorption due to its lipophilic characteristic. In this work, we had tested a αT nanoemulsion developed in our group after a single oral dose administration in C57BL/6J, SAMR1 and SAMP8 mice. After administration, mice were sacrificed and blood, liver, brain and lung samples were collected. Blood profile and tissue distribution of αT were analyzed by means of an optimized and validated LC-ESI-MS/MS method. The results revealed that the nanoemulsion increase αT levels in plasma, serum and liver compared to free αT and the senescence mice model (SAMP8 and SAMR1) present higher concentration of αT compared to C57BL/6J mice. However, as expected the results obtained in brain samples were completely different. In all groups of mice αT levels remained constant, none of the formulations administrated managed to increase αT concentration after a single dose administration. Considering that the development of nanostructures has made possible to increase the bioavailability of these compounds in blood and liver, further studies are needed to increase αT concentration in the brain in order to improve the neuroprotection through chronic administration.

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PS5-66

Studying the relevance of human APOE polymorphism in Alzheimer's disease through the application of iPSCs

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Alzheimer´s disease (AD), which is characterized by progressive neurodegeneration, is the most common form of dementia. The ε4 allele of gene encoding apolipoprotein E (APOE gene) is the strongest genetic risk factor for AD among the three polymorphic alleles (APOE- ε2, APOE- ε3 and APOE- ε4). Increasing evidences have shown that APOE4 is associated with diverse aspects of AD pathogenesis, but the impact of different alleles on human astrocyte and neuronal differentiation, maturation and function remains to be fully elucidated. In order to clarify these questions, we obtained induced pluripotent stem cells (iPSCs) from fibroblasts of AD patients carrying the ε3 and ε4 alleles (in homozygosis) and from healthy patients. These iPSCs were fully characterised and their undifferentiated and pluripotent nature was confirmed. We also used gene-edited iPSC lines homozygous for the main APOE variants and an APOE knock-out line. Astrocytes and neurons were generated from human iPSCs by establishing differentiation protocols through the sequential addition of different small molecules and growth factors. iPSCs-derived astrocytes expressed typical markers (GFAP, GLT1, AQP4 and S100ß) as well as APOE and they exhibited functional features such as glutamate uptake capacity, calcium waves production and inflammatory stimuli response. iPSCs-derived neurons expressed neuronal markers (MAP2, TBR1, vGLUT, Calbindin, GABA) and showed a functional profile. APOE4 neurons displayed signs of degeneration confirmed by the release of amyloid-beta and increased levels of phospho-Tau. These findings support the use of iPSCs-derived astrocytes and neurons as cellular models to investigate mechanisms of degeneration in AD and the connection between APOE and AD pathology.

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Intermediate alleles in HTT gene may play a role in sporadic tauopathies

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In Huntington´s disease (HD), the pathological condition occurs when the number of repeats exceeds a critical threshold (>35 CAG). However, sometimes these expansions remain within an intermediate range (27-35 CAG), denominated intermediate alleles (iaHTT), normally associated with normal phenotype. We previously analysed the association between iaHTT and neurodegenerative diseases other than HD. Interestingly, we found that the frequency of iaHTT is significantly higher among Alzheimer´s disease patients (AD; n=1126) regarding control subjects (n=509) (6.03% vs. 2,9%, respectively), suggesting that iaHTT might have a role in the pathogenesis of AD. Additionally, in a cohort of frontotemporal lobar degeneration patients (FTLD; n=225) there was an increased frequency of iaHTT regarding controls (5.3% vs. 2.9%), although the association was not statistically significant. Thus, the first aim of this study was to increase the number of the FTLD cohort. Therefore, we analysed the presence of iaHTT, by blood cells genotyping, in 440 FTLD patients. Although we found a nonsignificantly increased frequency of iaHTT in FTLD patients, results organization by clinical subgroups revealed that only progressive nonfluent aphasia subjects (PNFA) showed a significant difference of iaHTT regarding controls (13.6% vs. 2.9%, respectively). These data suggest that the presence of iaHTT may play a role in the development of tauopathies, such as AD and PNFA, since no association was found in Parkinson's disease patients (n= 610). The second aim was to determine whether the presence of iaHTT implies the existence of HTT protein aggregates in patients with tauopathy. To this end, we performed sequential biochemical fractionation of protein aggregates in post-mortem amygdala samples from both iaHTT AD and FTD patients, and their corresponding controls. Immunoelectron microscopy studies suggest that, in iaHTT patients, small HTT aggregates may exist in the same fractions where positive phosphorylated Tau protein filaments are present. Further studies are needed to determine whether the presence of iaHTT alters the physiology of Tau or other toxic proteins, which could explain its role as a pathogenic risk factor.

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PS5-68

Gene-Regulatory Dynamics of Microglia States during Neuroinflammation

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Gene expression and genetic variation studies suggest an important contribution of microglia cells to the onset and progression of most prevalent neurodegenerative conditions, such as Alzheimer's disease (AD), where a putative diversity of microglia states with divergent homeostatic or pathophysiological roles has been proposed. However, very little is known on the mechanisms regulating the ability of these highly plastic cells of the brain to adopt specialized roles when exposed to different conditions. Here, we combine high-throughput genomics and in situ RNA expression analysis at the single-cell level with functional assays to reveal the molecular underpinnings of the transitions and maintenance of the distinct phenotypic and functional states of brain's innate immune cells through the initiation, activation and resolution of the neuroinflammatory response. These data deepen our understanding of microglia heterogeneity which is critical to devise new therapeutics for most prevalent neurodegenerative diseases.

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PS5-69

MiR-138 as a restorative therapy for spinal cord injury

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Injury of the spinal cord triggers a set of damaging events that spread cell death to unaffected tissue. Apoptosis among spinal neurons begins few hours after injury and proceeds during weeks. On the other hand, injury to the spinal cord (SCI) alters the local expression of multiple microRNAs. These are short RNA sequences that inhibit the expression of hundreds of genes to regulate cell state and fate. MicroRNA-based therapies for SCI are currently under study because the available evidence indicates that microRNA dysregulation contributes to the onset of processes such as astrogliosis. Previous in silico analysis showed that miR-138-5p, a microRNA highly enriched in the central nervous system, targets components of apoptotic cell death pathways, such as caspase-3, caspase-7 and Bak-1.

We hypothesize that miR-138-5p downregulation after SCI contributes to the overexpression of apoptotic genes, therefore sensitizing neurons to death, and that a therapy restoring physiologic levels of miR-138-5p will reduce neuronal apoptosis after SCI. The aims of this work are to evaluate the changes in expression of miR-138-5p and its apoptotic targets and to test the neuroprotective effect of miR138-5p overexpression. To accomplish these objectives we used histological, cellular and molecular methods to measure miR-138-5p and protein expression in neurons after damage.

Gene expression data reveals that downregulation of miR-138-5p during the first week after injury coincides with the upregulation of apoptotic proteins. In situ hybridizations of spinal cord samples reveal that miR-138-5p is highly expressed in neurons and it is downregulated after SCI, particularly evident among neurons in the perilesional regions. Finally, the transfection of miR-138-5p mimic in primary neuronal cultures reduces the effector caspases activity and is neuroprotective against apoptosis induced by L-glutamic acid.

Our results suggest that a miR-138-5p-based therapy may be a potential candidate as treatment of SCI.

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PS5-70

Inhibition of Receptor Protein Tyrosine Phosphatase β/ζ prevents decreases on hippocampal neurogenesis induced by acute ethanol in male and female adolescent mice but only decreases ethanol intake in male mice

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Pleiotrophin (PTN) is a cytokine that has been shown to modulate ethanol drinking and reward. PTN modulates neuroinflammation in different contexts. PTN is an endogenous inhibitor of Receptor Protein Tyrosine Phosphatase (RPTP) β/ζ. Pharmacological inhibition of RPTPβ/ζ reduces binge-like drinking in mice. We hypothesize that RPTPβ/ζ also plays a role in chronic ethanol consumption and in the neural alterations associated with ethanol.

Male and female adolescent C57BL/6J mice were used in an intermittent access to ethanol (IAE) model using a 2-bottle choice protocol. Before each drinking session, mice received an administration of MY10 (60 mg/kg, i.g.), a small-molecule inhibitor of RPTPβ/ζ, or vehicle as control, and ethanol consumption was measured. At the end of the 4-weeks IAE protocol, brains were removed for immunohistochemistry analysis of Iba-1, GFAP and doublecortin (DCX). In the acute ethanol experiments, mice were treated with MY10 one hour before the administration of 6 g/kg ethanol (i.p.). Eighteen hours after ethanol administration, brains were dissected and subjected to the same immunohistochemistry analysis.

Male mice treated with MY10 drank less ethanol than controls and showed a reduced preference for the ethanol solution in the IAE model. In contrast, MY10 did not seem to have relevant effects on ethanol intake in female mice. This effect of MY10 was not accompanied by significant alterations in glial responses. In acute ethanol experiments, we observed an overall increased activation of microglia in female adolescent mice, especially in those treated with MY10 and ethanol. Acute ethanol induced a significant decrease on hippocampal neurogenesis in both male and female adolescent mice, which was completely prevented by pre-treatment with MY10 in both sexes.

In summary, inhibition of RPTPβ/ζ significantly reduced ethanol consumption in the IAE model only in male mice. RPTPβ/ζ critically modulates ethanol-induced decreases on hippocampal neurogenesis in both male and female adolescent mice.

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PS5-72

Targeting mTOR/4E-BP1 axis by the antidepressant Sertraline ameliorates motor deficits in the R6/1 mouse model of Huntington's disease

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Huntington's disease (HD) is a dominant inherited neurodegenerative disorder caused by an unstable expansion of a CAG repeat within the exon 1 of the huntingtin (HTT) gene. Early symptoms include psychiatric alterations as depression or irritability that progressively add up to cognitive and motor alterations in later stages, both related to dysfunction in hippocampal and corticostriatal pathways. Previous results from our group suggest that an aberrant increase in translation in the striatum of HD contributes to the pathophysiology. This hypothesis is well-supported by the amelioration of the characteristic motor deficits in the R6/1 HD mouse model as a consequence of the normalization of translation by intracerebral injection of 4EGI-1, an inhibitor of a protein synthesis initiation complex. Here, we show that striatal neuronal cultures from R6/1 mouse recapitulate translational alterations present in the adult striatum providing a model for drug screening. We took advantage of this to understand the molecular mechanism underlying aberrant translational control and to assess the ability of Sertraline, an antidepressant known to act as an inhibitor of the mTOR/4E-BP1 axis, to restore protein synthesis levels in the HD molecular context. In the same line, we used intraperitoneal administration of Sertraline to normalize the translation rate in the striatum of R6/1 mice, leading to the amelioration of motor learning and coordination deficits. Accordingly, these results suggest a potential new use of the antidepressant Sertraline for the treatment of motor symptoms in HD.

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PS5-74

Chronic pain induces plasticity into Locus coeruleus over time: role of the Locus Coeruleus - Dorsal Reticular Nucleus Pathway.

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Chronic pain triggers maladaptive brain and spinal remodelling leading to emotional disorders. Locus coeruleus (LC) is the main source of noradrenaline in the CNS and although its role in the descending inhibition of acute pain is well established, its contribution to pain facilitation has been also reported. One of the nuclei that receives noradrenergic projecting is the dorsal reticular nucleus (DRt) which has a pronociceptive role. Thus, we hypothesized that the LC→DRt pathway is involved in the pathological nociception associated with chronic pain. Using the chronic constriction injury of the sciatic nerve (CCI) as a model of neuropathic pain in, we evaluated time-dependent plasticity (from 2, 7 and 30 days after surgery) of the ipsilateral (LCipsi) and contralateral (LCcontra) LC through pharmacologic and chemogenetic approaches. Microinjection of lidocaine intra-LCipsi only increased cold and mechanical hypersensitivity in the CCI-2d group and not later. By contrast, microinjection of lidocaine intra-LCcontra reduced cold and mechanical hypersensitivity only in the CCI-7d and CCI-30d groups and not earlier. Additionally, lidocaine blockade of the LCipsi or LCcontra reversed pain-induced depression in the CCI-30d group. Furthermore, we observed an enhanced pCREB expression in the DRtcontra but not in the DRtipsi of CCI-30d animals. In this line, we evaluated the inhibition of the LCcontra→DRtcontra pathway using chemogenetics approaches in CCI-30d. The results showed a robust analgesia in evoked and spontaneous pain. However, the inhibition of the LCcontra→DRtcontra pathway did not relieve the depressive-like behavior in CCI-30d animals. Interestingly, the inhibition of this pathway induced depressive-like behaviour in sham animals. Overall, we demonstrated that unilateral nerve injury activates the LCipsi in the short-term, which temporally dampens the neuropathic phenotype. However, long-term pain triggers a bilateral LC activation and specifically, to the contralateral LC→DRt ensemble, contributing to chronic pain and the associated depressive-like phenotype.

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PS5-75

MiR-182-5p and miR-138-5p regulate Nogo-A/Nogo receptor expression, promoting neurite outgrowth in neural cells

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During postnatal development, central nervous system (CNS) neurons lose their ability to regenerate in part due to the presence of myelin-derived inhibitors of neurite outgrowth and neuroregeneration. Nogo-A is the most important myelin-associated inhibitor in CNS. This protein is expressed on the surface of oligodendrocytes and mediate the inhibition of axonal outgrowth through binding to its receptor, Nogo receptor (NgR), located in CNS neurons. The activation of this pathway at lesion sites may explain the lack of axonal regeneration in the CNS after trauma in adult mammals. Previous studies have shown that blockage either Nogo-A or NgR leads to growth cone formation and promotes neurite outgrowth.

MicroRNAs (miRNAs) regulate important processes in CNS such as neuronal differentiation, neuritogenesis, excitation, synaptogenesis, and plasticity. Two of these miRNAs are miR-182-5p (miR-182) and miR-138-5p (miR-138). Studies demonstrated that miR-182 promotes axonal growth and regulates neurite outgrowth via the PTEN/AKT pathway in cortical neurons, whereas miR-138 regulates axon growth during development and regeneration by targeting SIRT1.

In this study, we used luciferase reporter assays to demonstrate that miR-182 and miR-138 target Nogo-A and NgR mRNAs, respectively. Accordingly, both miRNAs downregulate the protein expression of their targets in different neural cell lines, such as Neuro-2a, C6 and PC12. Furthermore, we demonstrate that both miRNAs promote neurite outgrowth of neural cells in vitro. Specifically, the co-culture of miR-182 transfected C6 cells with rat primary hippocampal neurons increased neurite length of neurons in comparison with its negative control miRNA. Moreover, NgR downregulation by miR-138 in PC12 cells also increased neurite lengths. In conclusion, these miRNAs could be a potential miRNA-based therapy for the treatment of CNS traumatic injuries such as spinal cord injury.

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PS5-76

NeuroCLUEDO: which, when and where neurons die after spinal cord injury?

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Neuronal death is a central event of spinal cord injury (SCI) pathophysiology and a major determinant of the resulting functional deficits. Neuronal loss depends on features of the injury (type, severity, location), on the temporal and spatial context relative to insult, and on specific features of the neurons. Multiple articles have quantified neurons in the damaged spinal cord using different approaches but there is neither access to the original images nor a reference method for neuron detection after SCI. Here we present NeuroCLUEDO, an Open Science Framework repository aimed to determine which, where and when do neurons die after SCI. NeuroCLUEDO comprises a documented image repository of spinal cord sections stained with neuronal markers, test benchs for comparing methods in the naïve and injured spinal cords, and repositories of the obtained results. In the first analysis at NeuroCLUEDO we have uploaded raw images from a study of our laboratory testing the effects of a neuroprotective drug (ucf-101) in a mice model of traumatic SCI and use them to compare the effects of employing manual-, semiautomatic- and AI-based methods of cell detection on the number and location of identified neurons. Results from the analysis of 20 full sections of naïve, contused and treated mice spinal cords reveal that the number of identified neurons broadly agrees among the compared methods but that agreement is very poor concerning their position, that is, methods are not counting the same neurons despite the total number is similar. Interestingly, the comparison of manual identification data from different researchers revealed limited repeatability and reproducibility in both the number and position of the neurons. Both the repository and the test bench are open to anyone and contributions either as manual identifications or as new identifications methods are welcome.

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PS5-77

CALCIUM TRANSPORT AT ER-MITOCHONDRIA CONTACT SITES IS MODULATED BY PYK2

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Mitochondria-associated membranes (MAMs) are specialized compartments where ER and mitochondria closely interact. These regions are known to enable calcium effluxes from the ER to the mitochondria via the IP3R3-VDAC1 complex, reinforced by Grp75. Interestingly, genes encoding for IP3R3 and Grp75 have been suggested as genetic risk factors for schizophrenia. Moreover, DISC1, a schizophrenia related protein, has been shown to localise at MAMs and to regulate calcium transport.

On the other hand, Pyk2 is a non-receptor tyrosine kinase protein enriched in the hippocampus and has also been proposed as a genetic risk factor for schizophrenia. Pyk2 can be activated by calcium-dependent mechanisms and can translocate to mitochondria upon neuronal activation. Furthermore, we have previously observed that Pyk2 modulates mitochondrial dynamics in hippocampal neurons.

In the current work, we tested whether Pyk2 could have a role in the regulation of MAMs calcium transport. First, we observed by electron microscopy that Pyk2 is present both in mitochondria and in MAMs. Next, we used full Pyk2 knockout mice (Pyk2-/-) to analyse levels of MAM-resident proteins in brain tissue by Western Blot. Moreover, we obtained Pyk2-/- neuronal cultures to evaluate ER-mitochondria contact sites and calcium homeostasis. Cell live imaging experiments showed that Pyk2-/- neurons present an impaired calcium retention, suggesting that both ER and mitochondria compartments are affected. Finally, we explored the implication of MAMs in the pathology of schizophrenia by biochemical analysis of post-mortem brain samples of schizophrenic patients.

Taken all together, our results point out that Pyk2 could be highly relevant in the modulation of ER-mitochondria calcium efflux, hampering mitochondrial function.

PS5-78

Modeling Parkinson's Disease With the Alpha-Synuclein Protein

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The aggregation of alpha-synuclein (α-Syn) in form of Lewy bodies and neurites is the main neuropathological hallmark of Parkinson's disease (PD). PD is characterized by the loss of dopaminergic neurons in the substantia nigra. Precisely, the dysfunctionality and degeneration of these neurons is associated with α-Syn aggregation. Moreover, mutations in the SNCA gene, which encodes α-Syn, cause familial forms of PD and are the basis of sporadic PD risk. Animal models that reflect the dopaminergic neuronal loss and the widespread and progressive α-Syn aggregation constitute a valuable tool for studying the molecular mechanisms of the disease and might contribute to the development and validation of new therapies. Here, we summarize the main features of the α-Syn protofibrils (PFFs) models and recombinant adeno associated viral vector (rAAV) mediated α-Syn overexpression models, providing a detailed comparative analysis of both models. To characterize these PD models, we use SNCA-OVX mice injected with human PFFs of α-Syn and wild type mice injected with viral particles containing human mutated E46K α-Syn. Our results show that injection of α-Syn PFFs and overexpression of α-Syn mediated by rAAV lead to a different pattern of PD pathology in rodents. First, α-Syn PFFs model lead to the formation of Lewy body-like inclusions in brain regions directly interconnected with the injection site, suggesting that there is an inter-neuronal transmission of the α-Syn pathology. In contrast, rAAV-mediated α-Syn overexpression in the brain limits the α-Syn aggregates within the transduced neurons. Second, phosphorylated α-Syn inclusions obtained with rAAV are predominantly nuclear with a punctate appearance that becomes diffuse along the neuronal fibers, whereas α-Syn PFFs model lead to the formation of cytoplasmic aggregates of phosphorylated α-Syn reminiscent of Lewy bodies and neurites.

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PS5-79

Acute effects of intermittent theta-burst stimulation in the remediation of impulsivity in hypersexual Parkinson's Disease.

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Hypersexuality in Parkinson's Disease (PD+HS) is a form of impulse control disorder (ICD) characterized by excessive and hard to resist urges to engage in sexual-related activities that can arise in up to 7% of patients under dopamine agonists. Disruption of corticolimbic circuitry including pre-supplementary motor area (pre-SMA) has been linked to impaired inhibitory control in ICD. To date, clinical management for reducing ICDs-related behavior consists of reducing dopaminergic drugs at the expense of worse motor functioning. We aimed to use a repetitive transcranial magnetic stimulation protocol with excitatory effects over targeted circuits known as intermittent theta-burst stimulation (iTBS) to modulate the corticolimbic circuitry and consequently improve behavioral control using an erotic stop-signal task. A single-blind randomized controlled trial consisting of two stimulation sessions (real/sham) was designed. We stimulated over the pre-SMA in 19 PD+HS patients. Additional neurophysiological and neuropsychological variables were collected to characterize the cortical signature in ICD and their cognitive profile. We designed a modified version of a stop-signal task that included erotic and non-erotic stimuli to elicit sexual desire. In a single trial, after the presentation of visual stimuli, patients were asked to either press a key to a right of a left-pointing arrow or to withhold their response upon presentation of a cross. In total, 16 PD+HS were included in the final analysis. After real iTBS stimulation, PD+HS patients responded significantly faster in go signal reaction times ($p = 0.01$). Interestingly, improvements in stop-signal reaction times (SSRT) only reached significance for erotic stop trials ($p = 0.03$). Excitatory neuromodulation of pre-SMA using iTBS might prove beneficial for remediating impulsivity-related failures to control unwanted actions in PD. Further studies are necessary to clarify the potential therapeutic role of iTBS for treating hypersexuality and other subtypes of ICDs in PD and other neurocognitive and neuropsychiatric disorders.

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PS5-80

Small RNAs derived from differentially affected brain regions of Huntington's disease patients recapitulate diverse neuropathological outcomes in wild-type mice

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Progressive motor alterations and selective death of medium-sized spiny neurons in the caudate and putamen are key pathological hallmarks of Huntington's disease (HD), a neurodegenerative disorder caused by a CAG trinucleotide repeat expansion in the coding region of the huntingtin (HTT) gene. Most research has focused on the pathogenic effects of the resultant protein product(s); however, growing evidence indicates that expanded CAG repeats within mutant HTT mRNA and derived small CAG repeat RNAs (sCAG) participate in HD pathophysiology. The individual contribution of protein versus RNA toxicity to HD pathophysiology remains largely uncharacterized and the role of other classes of small RNAs (sRNA) that are strongly perturbed in HD is uncertain.

Here, we show that sRNA produced in the putamen of HD patients (HD-sRNA-PT) are sufficient to induce HD pathology in vivo. Moreover, sRNA obtained from the motor cortex (as an affected region) or from the cerebellum (as a less-affected region) are able to differently compromise motor function in wild-type mice. This observation prompted us to identify which sRNA species are enriched in HD putamen and present neurotoxic potential. We detected high levels of tRNA fragments (tRFs) in HD putamen, and we validated the neurotoxic potential of an Alanine derived tRF in vitro. These results highlight that HD-sRNA-PT are neurotoxic, and suggest that multiple sRNA species contribute to striatal neuropathology, favouring therapeutic strategies based on the blockage of sRNA-mediated toxicity.

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PS5-81

OLEOYLETHANOLAMIDE TREATMENT MODULATES NEUROINFLAMMATION AND MICROGLIOSIS IN A MOUSE MODEL OF CEREBELLAR NEURODEGENERATION

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The endocannabinoid oleoylethanolamide (OEA) has proven to exert anti-inflammatory and neuroprotective effects in different animal models with brain injury of varied etiology. Indeed, a previous study of our laboratory demonstrated that the exogenous administration of OEA -prior to the onset of the neurodegenerative process- resulted in neuronal protection of Purkinje cells and in an improvement of the behavioral defects observed in Purkinje Cell Degeneration (PCD) mutant mice.

In this study, we tested whether OEA treatment (10 mg/kg, i.p. at postnatal day 12) modulates neuroinflammation and counteracts microglial activation in the model of severe cerebellar degeneration PCD. First, changes in mRNA levels of proinflammatory, neurotrophic and neuroprotective factors were measured by quantitative PCR in both the short- (3- and 24-hours post-treatment) and the long-term (P30). Secondly, modulation of microglial activation and its phenotype was analyzed in parasagittal sections of cerebellar vermis by immunohistochemistry at P30.

Our results showed that OEA treatment significantly reduced mRNA levels of the proinflammatory factors IFNγ, IL1β and TNFα, and increased the neurotrophic/neuroprotective factors BDNF, GAP43 and MAP2 in cerebellum 3 and 24 hours after administration. Additionally, OEA decreased mRNA levels of IL1β and IL6 in the long term, which were upregulated in PCD mice at the age of P30. Finally, results from immunohistological analysis of cerebellar microglial cells showed that OEA administration reduced the microglial density in the cerebellum of PCD mice, which was exacerbated as a consequence of neurodegeneration. These findings demonstrate the neuroimmunomodulatory properties of OEA in the PCD mouse and shed light on the possible mechanisms of action of OEA as a therapeutic agent which could be a co-occurrence among down-regulation of neuroinflammation, modulation of microglial activation and neuronal protection.

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PS5-82

Cortical and hippocampal rhythmopathies in experimental models of brain metastasis

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Understanding the neurophysiology of brain tumours is critical to challenge the neurocognitive morbidity associated with the disease. Over recent years, several studies have shown alterations of neuronal network activity in peritumoral areas of primary brain tumours such as gliomas, with a bi-directional impact on cancer cells growth and on neural communication, which has been linked to hyperexcitability and seizures. However, the influence of brain metastasis on neural circuits remains relatively unexplored in spite of the high clinical prevalence of neurological symptoms. We evaluated neuronal activity from mice models of brain metastasis caused by local injection of melanoma, breast and lung cancer cells. By using multi-site silicon probes in peritumoral and contralateral areas of awake head-fixed mice, we measured the local field potential (LFP) in cortical and hippocampal areas. While control mice exhibited consistent laminar profiles of LFP signals, mice from the three models presented higher variability in the oscillatory power at different frequency bands. Animals with brain metastasis showed common impairments such as a generalized reduction of the oscillatory power at theta (4-12 Hz), alpha (9-14Hz), gamma (40-90 Hz) and high frequency oscillations (HFOs; >200 Hz) bands and reduced theta/delta (0.1-4Hz) ratio in cortical and hippocampal areas. Moreover, the hippocampal/cortical ratio for the HFOs band was significantly altered, suggesting an activity unbalance between both structures. Interestingly, we found several markers of hyperexcitability and seizures in some metastatic animals. Strikingly, we identified tumour-type specific alterations in the theta/delta ratio and the HFO frequency band, which did not depend on the size of the tumour mass. Our comprehensive analysis of these phenotypes includes not only neurons but multiple cell types of the metastasis-associated microenvironment, whose reactive state might indirectly contribute to interfere with brain homeostasis. Altogether, our data provide novel insights about the functional alterations associated with brain metastasis experimental models.

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PS5-83

From engrams to memory pathology in Down syndrome

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Recently, it has been proposed that memories are stored in a sparse subpopulation of neurons called engram cells, that become functionally connected during learning. The strengthening of their connections upon learning enable these cells to reactivate synchronically during memory recall. Thus, engram cells activated at the same time for a particular event would become the physical representation of the memory trace in the brain. Activity-dependent genetic tagging of engrams allows artificial reactivation or suppression of memories. We studied whether engram alterations can account for memory deficits in cognitive disorders. We propose that aberrant engram cells contribute to memory deficits in Down syndrome (DS), the most common form of intellectual disability. We found sparser neuronal activation during the acquisition of a contextual-fear memory in the hippocampus in a trisomic mouse model for DS (Ts65Dn), suggesting that less cells would be supporting a given memory. However, artificial reactivation of trisomic engram cells did not rescue the Ts65Dn memory deficits. We also found that astrocytes could contribute to memory deficits in Ts65Dn mice. Specifically, astrocyte activation using DREADDs depressed hippocampal synaptic transmission. Our results suggest that memory deficits in DS might be contributed by impaired “engram allocation”, in which new players, such as astrocytes might also participate.

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PS5-84

Pathological and therapeutic implications of myelin alterations in the Acid Sphingomyelinase Deficiency

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The myelin sheath is a modified plasma membrane that surrounds axons, providing support, protection and controlling the nervous conduction. Myelin is produced by oligodendrocytes (OLs) in the central nervous system, but myelination homeostasis depends not only on OLs but also on their active interplay with neurons, astrocytes and microglia. Myelin alterations occur in many lysosomal storage disorders (LSD). However, these deficits have been traditionally seen as a consequence and assigned to play a secondary pathological role. Acid Sphingomyelinase Deficiency (ASMD) is a prototypical LSD characterized, in its infantile neurovisceral form, by cellular accumulation of sphingomyelin and a rapid neurodegeneration that leads to death in early childhood. A recent study from our laboratory pointed to demyelination as the triggering factor for microglia dysfunction and neuronal death in ASMD. We have tested this hypothesis in the mouse model of ASMD, which lacks the acid sphingomyelinase (ASMko), by characterizing the myelin anomalies and their underlying molecular mechanisms.

Our results show that demyelination is a very early event in the cerebellum of ASMko mice that is accompanied by structural alterations in the myelin sheath. We also observed defects in the OL lineage resulting in an increased number of immature OLs. Experiments performed in primary cultures showed a defect in the radial and longitudinal growth of ASMko OLs, which show less and shorter processes than wt OLs due to sphingomyelin accumulation. Altogether, these results suggest that sphingomyelin-induced alterations in the OL differentiation may be at the basis of demyelination in ASMD. This information will enable us to preclinically validate strategies rescuing ASMko OL differentiation, which could open therapeutic perspectives for ASMD and other LSDs that share sphingomyelin storage, myelin alterations and neurodegeneration.

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PS5-85

Human amygdala involvement in Alzheimer's disease revealed by MALDI Imaging and SWATH analysis.

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Alzheimer's disease is characterized by executive dysfunction and memory impairment, underlying accumulation of extracellular amyloid-β and intracellular hyperphosphorylated tau. Amygdala atrophy have been shown to be pronounced in early stages of Alzheimer's disease, with correlation between the degree of atrophy and disease severity. Due to the early damage to the amygdala, personality changes often precede other clinical symptoms of the disease, such as cognitive impairment. Moreover, the amygdala constitutes a key that may contribute to the spreading of pathologic molecules due to its vast connectivity with other brain regions. These findings hypothesizing the amygdala as a central participant in Alzheimer's disease pathology. State-of-the-art -omic approaches would allow multilevel analysis but are currently underdeveloped. Proteomic studies on human tissue would be especially suitable to identify peptide fingerprint changes in human amygdala during pathology.

Post-mortem tissue was provided by IDIBAPS, BTCIEN, BIOBANC-MUR, BPA and NAVARRABIOMED Spanish National Biobanks. Experimental procedures were approved by Ethical Committee of Clinical Research at Ciudad Real University Hospital (SAF2016-75768-R and PID2019-108659RB-I00). A total of 16 cases were used for MALDI Imaging and SWATH analysis. Proteomic analyses consisted in PCA, heatmap, volcano plot and detection of activated/deactivated pathways. MALDI Imaging reflected differences in distribution of up/downregulated proteins identified by SWATH Analysis.

The study was sponsored by the UCLM/ERDF (2020-GRIN-29145 to NPND), Spanish Ministries of Economy and Competitiveness/ERDF (grant no. SAF2016-75768-R) and Science and Innovation (grant no. PID2019-108659RB-I00) to AMM and Autonomous Government of Castilla- La Mancha/ERDF (grant no. SBPLY/17/180501/000430) to AMM and DSS). MGR and SVC held a predoctoral fellowship granted by UCLM/ESF and VAL held an assistant professorship granted by UCLM/ERDF. Authors thank Dr. Pilar Alberdi (technical specialist UCLM/ERDF supported) her proteomic expertise.

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PS5-86

ApTOLL: A NOVEL REMYELINATING MOLECULE IN A MODEL OF MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a degenerative, autoimmune and chronic disease of the central nervous system (CNS) that constitutes the second cause of neurological disability in young adults. It is characterized by the loss of oligodendrocytes and, therefore, myelin, both in the white and in the gray matter. On the other hand, the autoimmune component that underlies the pathology of MS is the promoter of the processes of inflammation, demyelination, and damage to the axonal network, where the Toll-like type 4 receptor (TLR4) and proinflammatory signaling that triggers its activation plays a crucial role. In this sense, the innovative ApTOLL molecule has been developed with aptamer technology and seeks to antagonize the TLR4 in order to achieve an immunomodulatory and anti-inflammatory effect. ApTOLL is a single chain DNA aptamer that supposes a novel strategy, both for its molecular nature and for its mechanism of action, for the treatment of diseases with an important inflammatory component such as MS.

In this research, the immunomodulatory and remyelinating effect of four doses of ApTOLL (0.45 mg/kg, 0.91 mg/kg, 1.82 mg/kg, and 3.6 mg/kg) has been determined for the study of the therapeutic dose of this compound in the Experimental autoimmune encephalomyelitis (EAE) model of MS. A clear reduction in the clinical score of animals treated with ApTOLL with respect to the vehicle group is observed, as well as a greater area of myelin and neurofilaments in the spinal cord. Furthermore, this molecule seems to have a direct effect on the biology of oligodendrocytes precursors cells (OPCs) by promoting their proliferation and differentiation towards myelinating phenotypes. This effect combined with other possible neuroprotectors could be a highly innovative strategy that would cover all aspects of the ideal therapy for MS.

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PS5-87

Local protein synthesis in health and disease

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Neurons are able to respond to changes in their environment by producing proteins locally. Lopcal protein synthesis plays relevant roles in growth cone behavior and synapse formation during embryonic development, and in axon maintenance by regulating mitochondrial function in adulthood. Importantly, a role for local translation in mediating amyloid-induced neurodegeneration, a hallmark for Alzheimer´s disease, has recently been described. Although most localized mRNAs are believed to be transported to distal neurites (dendrites and axons) from the somatodendritic compartment, recent evidence suggests that some neuritic transcripts might be delivered to neurons by glial cells. Among the mechanisms proposed for this horizontal transfer, is the secretion extracellular vesicles (EVs) by glia and subsequent internalization into axons. These extracellular vesicles contain RNAs and proteins which might be involved in translation regulation.

One of our aims is to determine the contribution of glial EVs in the ability of neurites (axons in particular) to translate proteins locally in models of amyloid-induced pathology. Ultimately we wish to understand if EVs play a role in neurological disorders such Alzheimer´s disease, by regulating intra-axonal signaling events that require local translation.

Experiments performed in primary cultures thus far indicate that EVs from different origins (neuronal, glial, mixed.) elicit distinct effects on local translation depending on whether they are secreted by healthy cells or in the context of amyloid-induced pathology.

While analyzing the effect of glia on local translation in neurons we realized that glial cells (microglia in particular) was able to produce proteins locally. This event has only been recently reported in this cell type and its role in brain pathology has not been addressed. Thus, we established a second line of research in which we aim at deciphering the role of local protein synthesis in glia itself in nervous system physiology and pathology.

Here we summarize the results gathered so far in the context of the maion research lines of our lab.

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PS5-88

Enhanced neuronal glycolysis causes cognitive impairment and metabolic syndrome in mouse

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In contrast to the predominantly glycolytic nature of astrocytes, neurons use very little glucose to obtain energy through glycolysis (1). This is a critical metabolic signature of the brain that is dictated by differences in the abundances of the pro-glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3). Thus, PFKFB3 is highly expressed in astrocytes, but repressed in neurons due to a continuous proteasomal degradation after ubiquitination by the E3-ubiquitin ligase anaphase-promoting complex/cyclosome-Cdh1 (2). However, the in vivo physiological significance of the limited glycolytic activity of neurons is intriguing. To address this matter, here we generated a genetically engineered mouse to express PFKFB3 in neurons in vivo (CaMKII-PFKFB3). We found that neuronal PFKFB3 upregulated glycolysis, causing NAD depletion, dysfunctional mitochondria, redox stress and impairment of the autophagic flux in several brain regions, including the hippocampus and the mediobasal hypothalamus. Phenotypic characterization of these CaMKII-PFKFB3 mice revealed cognitive deterioration, motor discoordination, glucose intolerance and obesity. Interestingly, these biochemical and phenotypic alterations were rescued by abolishing redox stress via genetically expressing a mitochondrially-tagged isoform of catalase (mCAT) in neurons. Mechanistically, the increase in glycolysis shifted down glucose consumption through the pentose-phosphate pathway, causing redox stress that impaired mitochondrial respiration, triggering a signaling pathway leading to an aberrant positive loop of glycolytic activation. These data indicate that the existence of a low glycolytic activity in neurons is a natural mechanism aimed to sustain organismal welfare. [Funded by the Agencia Estatal de Investigación PID2019-105699RB-I00/ AEI / 10.13039/501100011033]. References: (1) Nat. Cell Biol. 6:45-51 (2004); (2) Nat. Cell Biol. 11:747-752 (2009).

PS5-89

Simultaneous reciprocal chemogenetic regulation of AgRP and POMC neurons reveals non-overlapping functions in control of metabolism.

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Hypothalamic neuronal circuits control energy metabolism, adjusting food intake and metabolic demands to match internal and external cues. Two neuronal populations reside in the arcuate nucleus of the hypothalamus with opposite roles: GABAergic AgRP neurons respond to negative energy balance, promoting rapid food intake and insulin resistance, while POMC neurons are activated in positive energy balance states, resulting in reduced food intake and increased energy expenditure. The coordination of these two population is critical for the metabolism homeostasis. Their feeding-state dependent opposite regulation has thus far not been modulated in vivo, since current approaches have focused on the isolated chemo- or optogenetic modulation of either cell population.

To simultaneously modulate the activity level of both neuron subtypes in opposing directions, as observed during their natural regulation, we employed the use of non interacting recombinases to simultaneously express the activatory DREADD receptor hM3DGq in a Cre-dependent manner in AgRP neurons, while POMC neurons expressed inhibitory hM4DGi receptor dependent on POMC-neuron specific Dre recombinase expression. This approach created a novel transgenic mice line that allows isolated or combined antagonistic chemogenetic modulation of both neuronal subtypes. These experiments revealed that food intake and substrate utilization are driven mainly by AgRP circuits, without further effects of simultaneous POMC neuron inhibition. However, systemic insulin sensitivity, liver sympathetic nerve activity, liver transcriptome profiles and gluconeogenic capacity are differentially modulated by the interaction of POMC and AgRP neurocircuits in comparison to their separated effects. All together, these results demonstrate that the interplay between the independent activation levels of AgRP and POMC circuits controls the metabolic regulation in peripheral tissues, suggesting non-overlapping functions governed by AgRP and POMC neurons.

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PS5-90

Non-viral vehicles and modified oligonucleotides for RNAi-based therapies for CNS damage

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Damage to the Central Nervous System (CNS) usually results in dramatic deficits due to the loss or alteration of neural circuits. Gene therapies can modulate key proteins and pathways to reduce damage, increasing the chances of enhancing functional recovery. MicroRNAs (miRNAs) are endogenous short oligonucleotides that regulate the expression of hundreds of proteins to control cell function in physiological and pathological conditions. Despite their potential, applying miRNA-based therapies is limited by difficulties to deliver RNAs to neural cells, due to their poor stability, poor efficiency of delivery, and off-target effects. Within this context, we have compared the potential of different polymer-based vehicles as well as different oligonucleotide modifications for miRNA-based therapies.

Polymeric vectors are an attractive approach due to their improved safety profiles, easy and cheap production, ease of synthesis and chemical versatility, and unlimited possibilities of modification. In this study, we have compared commercial vehicles with various functionalized poly-ethyleneimine (PEI) polymers and N-ethyl-pyrrolidine-methacrylamide copolymers. Our in vitro analyses demonstrate that functionalized PEI vehicles show the best performance when considering together RNA protection against nucleases, delivery to neural cells, endosomal escape, toxicity, and efficacy in Neuro-2a cells and rat E18 primary hippocampal neurons. On the other hand, analyses with modified oligonucleotides reveal that siRNA-like duplexes (i.e. fully complementary sense strand) incorporating 2-O-methyl and 1, 3- propanediol present increased stability against nucleases and better transfection performance than endogenous miRNA duplexes. Moreover, their conjugation with specific cyclic peptides can provide additional advantages, particularly eliminating the need for vehicles by conferring protection and providing cell-targeting specificity.

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PS5-91

Hippocampal-targeted, cell type-specific manipulation of NFκB activity to treat brain injuries and diseases

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NFκB is a major transcription factor that regulates a large number of genes during various biological processes, such as early development, cell survival, synaptic plasticity, memory functions, and various diseases, including brain damage, neuroinflammation and neurological diseases. In the central nervous system, many of those processes, such as memory formation, learning, control of anxiety, and cognitive functions, depend on the hippocampus. This brain region is profoundly affected in mesial-temporal lobe epilepsy (MTLE) and traumatic brain injury (TBI) models, where hyperexcitation and neuronal excitotoxicity cause gliosis, cell death, and aberrant neurogenesis. In those models, increased NFκB expression levels have been detected. In other models, as ischemic animal models, downregulation of NFκB activity reduces brain damage, whereas inhibition of NFκB activity promotes the severity of disease expression in models of spinal cord injury.
In order to evaluate the importance of NFκB in diseases that cause hyperexcitation in the hippocampus, we have developed adeno-associated viruses equipped with tetracycline controlled genetic switches selectively targeting astrocytes, microglia and neurons. By cell type specific inducible control of NFkB gene expression, we aim to investigate the role of NFkB in disease onset and progression, and possibly also protection.

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Modulating neuronal activity using phytochromes

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Optogenetics is a promising approach for the precise spatiotemporal control of biochemical processes in cells and animals. Recently, modulation of brain activity has been used to treat neurological diseases in human patients. However, opsin-based stimulation induces acute changes in neuronal activity but lacks long-term modulation. Instead, phytochromes, which are soluble photoreceptors present in plants and bacteria, can act as adenylate cyclase and produce cAMP in cells upon photoactivation. Within neurons, cAMP modulate metabotropic responses and induce many intracellular signalling pathways, including synaptic plasticity, leading to long-term cellular changes. Thus, light-induced modulation of cAMP might allow for a more sustained modulation of brain circuitry. Our main goal is to evaluate the potential of phytochromes to induce long-term neuronal activity in specific brain circuits. First, we explored in mouse primary cortical neuronal cultures how changes in cAMP levels modify spontaneous neuronal activity by performing calcium-imaging recordings before and after Forskolin application. Forskolin-induced cAMP caused an overall increase in calcium levels and modulated the network. We also evaluated the changes of cAMP levels induced by Forskolin in STHdhQ7/Q7 neural cells using cAMP fluorescent sensors Flamindo 2 and Pink Flamindo. Then, we infected 7 DIV primary cortical neurons with a custom made AAV-CamKII-DdPAC-Flag-tag and investigated the dynamics of phytochrome activation and deactivation, with 670 nm and 780 nm light, respectively. We used NETCAL software to analyze the Ca2+ changes and decode calcium-dependent neuronal activity. Our results indicate that we can successfully activate phytochromes in neurons and modulate their activity. We are currently implementing fiber photometry tools to study phytochrome effects in vivo. Altogether, these results contribute to the development of new approaches towards modulating brain activity and establishing phytochromes as a novel tool for optogenetic applications.

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PS5-93

Longitudinal calcium imaging of neural activity in epileptic networks: in-vitro an in-vivo approach

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Epilepsy is a neurological disorder characterized by recurrent epileptic seizures generated by dysfunctions in the neuro-glial circuitries. Seizures trigger a positive-feedback cascade of events that generate and perpetuate in one side gliosis, inflammation, cell death, in conjunction with neural patho-topological connections, aberrant synchronizations and hyperexcitability. Mechanisms are still poorly understood and the efficacy of treatments has not improved for decades.

We are working in complementary in-vitro/in-vivo experimental murine models which allow us to visualize and analyze neuronal activity in a longitudinal manner to monitor and deepen the mechanisms, in the same circuits and over time, behind the switch from physiological to pathological conditions, and additionally to check potential therapeutic approaches on the induced epileptic conditions.

In both systems, longitudinal monitoring of neural circuits' activity with single-cell resolution follows the initial genetic encoding of calcium sensors (specifically Gcamp6f) through viral vector injections.

In the in-vitro model, organotypic hippocampal cultures are cultured over weeks in control conditions and under temporary epileptogenic hyperexcitable conditions. Synchronizations, neural firing (frequency of calcium events) and functional connections can be characterized at different time points. Preliminary quantifications highlight increased neural firings and synchronizations in the neural circuits exposed to hyperexcitable conditions.

In the in-vivo model, we image longitudinally, in awake and behaving mice, hippocampal (or neocortical) circuit's activity through a state-of-the-art endoscope allowing single-cell resolution (Miniscope). Epilepsy is induced by a single injection of kainic acid (KA) into the contralateral hippocampus or the amygdala. Imaging over the same cells and circuit is performed chronically from physiological conditions (pre-KA-injection) to stabilized status epilepticus conditions (about ten days after KA-injection). Preliminary observations highlight the emergence of a variety of new patterns of functional connections and synchronizations in epileptic conditions.

The above methodology possibly opens new perspectives for testing mechanisms and the impact of treatment on the epileptic brain.

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Experimental and modeling study of near infrared-laser stimulation in single and electrically coupled neurons

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Near-infrared laser stimulation is a non-invasive stimulation technique for studying neural dynamics. This optical stimulus elicits changes in single neuron dynamics with little or no cell damage. However, the detailed biophysical basis of the effect of this stimulation is not yet known. In this work, we quantified the outcome of infrared laser stimulation both on single cells and on electrically coupled neurons. To explain the effect of the stimulation we employed a combined experimental and modeling approach in the nervous system of Lymnaea stagnalis. We first characterized the activity recorded with intracellular electrodes comparing the amplitude, duration, depolarization and repolarization slopes of individual spikes before, during and after the infrared-laser stimulation. In these experiments, the laser beam was focused on one of the neurons being recorded. Spike duration was reduced under the laser stimulation, along with a change in the repolarization slope. The effect was reversible after termination of the stimulation. The analysis was repeated on well-known electrically-coupled cells of the right parietal and visceral ganglia of Lymnaea. For electrically coupled cells, the activity was simultaneously recorded in both neurons while the laser was illuminating only one of them. The experimental protocols were reproduced in a conductance-based model that considered multiple explanations for the observed effect of the laser stimulation, and we tested which ones best reproduced all observations. Our study unveiled several factors underlying the source of the infrared-laser effect and supports the use of this stimulation in multiple experimental protocols.

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PS5-95

Gene variants involved in the glutamate and calcium pathway in the epileptic model hamster GASH/Sal.

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The GASH/Sal hamster is a genetic model of audiogenic epilepsy, in which the inferior colliculus (IC) is the epileptogenic focus. The GASH/Sal exhibits numerous gene variants that might contribute to the genetic influences for seizure susceptibility. The goal of this work was to determine the molecular significance of some gene mutations related to glutamate and calcium pathways detected when comparing the exome of the GASH/Sal hamster with that of the wild type (control). Sequencing techniques, RT-qPCR, three-dimensional protein structures, immunohistochemistry and Western blot allowed us to detect and validate single nucleotide polymorphisms (SNPs) in the genes coding the kainate receptor (Grik1) and the α2β3 subunit of the calcium channel CaV2.1 (Cacna2d3).

In silico analysis of the three-dimensional protein modeling revealed that the SNPs carry amino acid substitutions (S/P and H/Y) that might affect the intramolecular contact and stability of both proteins. The RT-qPCRs, immunohistochemical and Western-blot analyzes showed an increase in the gene and protein expression of Grik1 in the IC, as well as an increase in immunostaining for Grik1 and Cacna2d3 in the facial nucleus when compared the GASH/Sal with the counterpart controls. On the contrary, a significant decrease in gene and protein expressions was detected for both proteins in the cerebellum, hippocampus, and cortex. In sum, our study supports that the mutations detected in the Grik1 and Cacna2d3 genes are most likely to result in an excitatory unbalance in the IC that facilitates the status epilepticus.

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Sex differences of acute and chronic administration of cannabidiol in the genetically audiogenic seizure-prone hamster GASH/Sal

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Despite evidence supporting the use of cannabidiol (CBD) as an anticonvulsant agent, controversy remains related to dosage, sex-dependent efficacy, and negative health effects. Here, we aimed to investigate the potential anticonvulsant and adverse effects of CBD in the genetic audiogenic seizure hamster from Salamanca (GASH/Sal). Male and female GASH/Sal hamsters received acute and chronic intraperitoneal injections of CBD (200 mg/kg) or the vehicle and seizures were induced by loud sound stimulation. Animals were evaluated for seizure severity and neuroethology with the Ethomatic software, body weight variations as well as hematological and biochemical parameters (14-days post-treatment). Blood levels of CBD were assessed using HPCL in all experimental groups. Animals treated with the vehicle exhibited the maximum values in the categorized seizure index after acute and chronic administrations. Acute effects of a single CBD administration were the complete elimination or significant reduction of seizures in females, whereas males were not affected. Chronic treatment with CBD showed absence of seizures in 40% of the females and a significant decrease in seizure severity in another 40%. On the contrary, 12% of the males presented fully absence of seizures and 50 % reduced the seizure severity, whereas no effects were noticed for the remaining males. All GASH/Sal animals showed a steady weight as well as normal hematological and biochemical parameters after chronic administration, without statistically significant differences as compared to the baseline pre-treatment conditions. Higher blood levels of CBD correlated with reduced seizure scores. In sum, acute and chronic CBD treatments exert sex-dependent anticonvulsant effects on the GASH/Sal model. No adverse effects on body weight, hematological parameters and liver function were observed following repeated daily administration.