Poster Session 3: Thursday, 4th November, from 15:00 to 18:30, Exhibition Hall.

PS3-01

Calcium channels in synapse elimination during neuromuscular junction development

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During the development of the nervous system, synaptogenesis occurs in excess though only the appropriate connections consolidate. At the neuromuscular junction, competition between several motor nerve terminals results in the maturation of a single axon and the elimination of the others. The activity-dependent release of transmitter, and neurotrophic factors allow the direct mutual influence between motor axon terminals through receptors such muscarinic ACh autoreceptors (mAChRs) and the tropomyosin-related kinase B (TrkB). Thus, a multiple metabotropic receptor-driven downstream balance between PKA and PKC isoforms modulate the phosphorylation of targets involved in transmitter release and nerve terminal stability. A similar level of PKA inhibition and PKC potentiation would be required during development to promote synapse loss. We observed in the weakest endings on the polyinnervated NMJ that M1 subtype mAChR receptors reduce ACh release through the PKC pathway coupled to an excess of Ca2+ inflow through P/Q-, N- and L-type voltatge-gated calcium channels (VGCC).

Here, we investigate the involvement of the VGCC in synapse elimination during development. Selective VGCC blockers and activators were applied daily on the Levator auris longus (LAL) muscle surface from P5-P8 transgenic B6.Cg-Tg (Thy1-YFP)16 Jrs/J mice and the axon number and postsynaptic receptor cluster morphologic maturation were evaluated in P9 NMJ. We found that both L- and P/Q-type VGCC (but not the N-type) are equally involved in postnatal axonal competition and synapse elimination. The block of these VGCC or [Ca2+]i sequestration results in the same delay of axonal loss that the cPKCβI isoform block or PKA activation. However, nPKCε block results in a significant greater delay suggesting the involvement in this case of a calcium-independent mechanism. The involvement of the VGCC in the postsynaptic maturation seems more complex and some contribution of the N-type VGCC canot be discarded and merites further investigation.

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PS3-02

Effects of shortening the habituation protocol on exercise capacity during adolescence of rats

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The brain causal mechanisms working on peripheral tissues during a physical activity are poorly understood. In previous studies we developed a model to analyze motor responses based on a habituation program to exercise consisting of a progressive increase of the training load. This initial phase is determinant to improve motor performance during training programs in forced running conditions. Determine if shortening the habituation program modify responses in exercise capacity, and if this can be related with muscle peripheral adaptations.

Sessions of the habituation in forced running wheel were developed throughout 2, 4 and 8 days of training. Once the habituation phases were completed, rats were subjected to an incremental exercise test to determine the physical capacity. Samples of gastrocnemius and soleus were used for qPCR and Western blot analysis of markers involved in muscle adaptation.

The total time of running during the incremental test was of 37.78 ± 2.65 min for 8 days habituated rats but 15.84 ± 1.22 min for non-habituated rats (wheel control). In the case of 4 days habituated rats the total time of running was 36.02 ± 2.67 min with 17.35 ± 2.86 for the control. Finally, we found that after 2 days of habituation, rats run during the incremental test 28.95 ± 3.94 min, but 19.97 ± 2.57 min in the case of the control. We didn´t observed any differences in selected muscle markers in terms of mRNA molecules or protein concentrations justifying peripheral adaptations.

Shortening of habituation period to 4 days produce similar effect in the incremental test than 8-days habituation period. However, 2 days habituation period produce a decreased response during the incremental test compared with 4- and 8-day habituated rats. The differences in running can not be justified in terms of muscle peripheral adaptations, strengthening a central nervous system effect.

PS3-03

Development of Otp and Sim1 cells in the chicken extended amygdala

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The amygdala is recognized as the master regulator of the stress response and plays a key role in social behaviour and cognition. Using cell-specific functional mapping, it has been shown that, in the mouse extended amygdala, different types of GABAergic neurons are involved in this regulation. These neuronal subtypes originate in different embryonic divisions of the subpallium. Using an evodevo approach, homologous cells have also been found in chicken. However, the extended amygdala of mouse and chicken also includes glutamatergic neurons. In mouse, some of these glutamatergic cells express the transcription factors Otp or Sim1. The Otp cells mostly populate the medial extended amygdala and were initially thought to originate in an Otp-expressing domain of the alar hypothalamus. However, our laboratory recently showed that most of these Otp glutamatergic cells also coexpress the telencephalic transcription factor Foxg1, and originate in a distinct telencephalon-opto-hypothalamic embryonic domain (TOH), at the border between telencephalon and hypothalamus. In addition, Sim1 cells originate in the alar hypothalamus and migrate to other parts of the amygdala. In this project, we investigated whether similar Otp and Sim1 cells are found in the chicken amygdala. To that aim, we performed double labeling of in situ hybridization for Otp or Sim1, and immunohistochemistry/immunofluorescence for Foxg1 in the chicken brain. Our results demonstrate: 1) The existence of a TOH domain in chicken, coexpressing Otp/Sim1 and Foxg1, that produces cells for the medial extended amygdala. 2) A subset of Sim1 expressing cells that seems to migrate from the alar hypothalamus to the capsular part of the central extended amygdala. These findings open the venue for further studying the connections and functions of these different neuronal subtypes and their relation to the GABAergic cells of the extended amygdala.

Funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 812777

PS3-04

Analysis of the activation dynamics of postnatal neural stem cells of the subventricular zone using in utero electroporation

Ms. Isabel Mateos-White[1], Mr. Jaime Fabra-Beser[1], Mr. David de Agustín-Durán[1], Dra. Isabel Fariñas[1], Dra. Cristina Gil-Sanz[1]

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The subventricular zone (SVZ) of the lateral ventricles is one of the neurogenic niches of the adult mammalian brain. Neural stem cells (NSCs) populating this niche are pre-specified since early embryonic stages, but they remain quiescent until its postnatal reactivation. At this time, they give rise to different types of interneurons that migrate through the rostral migratory stream (RMS) to populate the olfactory bulb. Although many studies have been carried out in the last years characterizing the particular cellular behaviour of these NSCs, important questions are still open including their activation dynamics throughout the postnatal period. Building on the embryonic specification of NSCs, we can target them using in utero electroporation. This method allows in vivo DNA transferring in order to label, analyze fine cell morphology or conduct functional experiments to perturb the expression of genes of interest, among other approaches. In the present work, we analyze the activation dynamics of NSCs in the SVZ since early ages of postnatal development until adulthood implementing lineage-tracing studies by in utero electroporation in Cre-reporter mice.

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PS3-05

Conserved cell types in the early embryonic brain across vertebrates

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The "phylotypic" denomination of pharyngula embryonic stage arises from being considered as the most conserved developmental period across species from a given phylum. The evolutionary similarities in the phylotypic stage have long been observed morphologically and have also been confirmed transcriptionally in the last decade. At this intermediate point in development, segmentation and organogenesis processes stablish a phylum-wide common body-plan or bauplan. This simultaneous early formation of multiple organs is thought to be governed by a common set of phylotypic genes, which are evolutionarily conserved due to their pleiotropy. In the brain, most of these patterning genes are historically known to contribute to primordial, widely conserved neural structures development. Nonetheless, inter-species comparisons beyond individual master genes are still challenging considering the lack of in-depth brain transcriptomic data at cell type level. To overcome this shortage, we performed single cell transcriptomics analysis of the phylotypic brains from representative vertebrata species: mouse (Mus musculus), chicken (Gallus gallus), gecko (Paroedura picta) and zebrafish (Danio rerio). Added to our current neuroanatomical knowledge and in situ hybridization assays, this ground-breaking tool allowed us to map the cell types that comprise the phylotypic brains of these species and compare their gene expression levels. Therefore, these transcriptomic brain atlases from several species not only complement current evolutionary neural cytoarchitectonic knowledge, but also provide deeper insights of cell type homologies across vertebrates. In conclusion, our results confirm the existence of an ancestral phylotypic brain and sheds light on the reasons why its cell types have been barely modified for over 500 million years despite thereafter speciation events in vertebrata.

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PS3-06

Unravelling the Neural Cell Progeny of Single Subpallial Progenitor Cells

Ms. Rebeca Sánchez-González[1], Dr Laura López-Mascaraque[1]
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Over the last decades a growing body of studies has provided evidence for the heterogeneity of neural progenitor cells (NPCs). Distinct subsets of progenitor cells are destined to become lineage-restricted while others function as bi/multipotent providing a molecular and functional diversity of their neural lineages. The multi-color genetic lineage tracing system, UbC-StarTrack, allows an independent tracking of sister clones derived from a common targeted progenitor under in vivo conditions. As a result, we designed different StarTrack strategies to permanently label individual progenitor cells and their progeny accordingly with the identity of the NPCs (Sánchez-Gonzalez et al 2020a). In particular, we used the UbC-(Gsh-2-hyPB)-StarTrack, with a PiggyBac transposase under the expression of Gsh-2 promoter (Sánchez-González et al., 2020b), now enabling to specifically target progenitor cells located in the ventricular surface of the mouse embryonic subpallium (ventral area of the telencephalon). The derived-cell progeny of those early embryonic subpallial progenitors produced the different neural types: astrocytes, oligodendrocytes, NG2 and even neurons. In addition, this strategy allowed us to perform an accurate analyses of the clonal relationships between the derived-cell progeny of those targeted individual subpallial progenitors, that could generate daughter cells of different lineages.

Our findings illustrate the degree of progenitor heterogeneity, particularly considering the molecular and functional diversity of their cell-derived progeny. Moreover, data revealed the lineage relationships of individual subpallial progenitors and their daughter cells, that might help to gain new insights into their behavior, complexity and functionality.

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PS3-07

Understanding the mechanisms involved in migration and circuit integration of thalamic interneurons

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GABAergic interneurons (INs) are inhibitory cells necessary to balance excitation and inhibition in the brain. During development, INs migrate from their site of origin towards their final destination, where they build stable neural circuits together with the excitatory cells. Thus, our aim is to unravel the mechanisms that direct INs migration and circuit assembly in the mouse thalamus. We specifically investigate, first, the role of thalamic activity on INs migration and integration, and second, to what extent the abnormal embryonic thalamic activity affects the distribution of cortical interneurons. We have seen changes in the number of dorso lateral geniculate nucleus (dLGN) INs in mice lacking embryonic thalamic spontaneous activity, and strikingly, changes also in the density and morphology of microglia. In addition, in primary sensory cortices, the proportion of Somatostin-positive and Parvalbumin-positive INs varies between mice lacking thalamic spontaneous activity and control littermates. Thus, normal patterns of thalamic spontaneous activity appear to contribute to the circuit assembly both in the thalamus and in the cortex.

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PS3-08

Differential expression levels of Sox9 in early neocortical radial glial cells regulate the decision between stem cell maintenance and differentiation.

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Radial glial progenitor cells (RGCs) in the dorsal telencephalon directly or indirectly produce excitatory projection neurons and macroglia of the neocortex. Recent evidence shows that the pool of RGCs is more heterogeneous than originally thought and that progenitor subpopulations can generate particular neuronal cell types. Using single cell RNA sequencing, we have studied gene expression patterns of RGCs with different neurogenic behavior at early stages of cortical development. At this early age, some RGCs rapidly produce postmitotic neurons, whereas others self-renew and undergo neurogenic divisions at a later age. We have identified candidate genes that are differentially expressed between these early RGCs subpopulations, including the transcription factor Sox9. Using in utero electroporation, we demonstrate that elevated Sox9 expression in progenitors affects RGC cell-cycle duration and leads to the generation of upper-layer cortical neurons. Our data thus reveal molecular differences between progenitor cells with different neurogenic behavior at early stages of corticogenesis and indicates that Sox9 is critical for the maintenance of RGCs to regulate the generation of upper layer neurons.

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PS3-09

Lineage Cell-Potential of Single Neural Progenitor Cells

Ana Cristina Ojalvo-Sanz[1,2], Rebeca Sánchez-González[1], Laura López-Mascaraque[1]
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The assemble of the brain from a pool of Neural Progenitor Cells (NPCs) is a complex process. Increasing evidence supports the heterogeneity of NPCs across and within distinct brain regionsand their importance for the generation of the different neural types. Some studies suggest that progenitor diversity is more restricted to one specific lineage whereas others show a potential cell diversity depending on the spatio-temporal patterning. Neural stem cells give rise to transient progenitors termed neuroepithelial cells that generate Radial Glial Cells (RGC), multipotent progenitors that produce, in overlapping waves, neurons, astrocytes, NG2-glia and oligodendrocytes. However, although RGCs are the most known cortical NPCs, NG2-glia (or NG2-cells) is another remarkable cell type that can also act as a progenitor. In the adult mouse brain NG2-glia is able to generate OLs, Astrocytes or even Neurons. Moreover, our previous works revealed the existence of NG2-progenitors during development, enable to produce different neural cell lineages depending on the embryo stage.

To elucidate the cell potential of single-NPCs, my lab developed the UbC-StarTrack a multicolor genetic tool that allow us to tag single progenitors with stable and heritable labelling.This strategy, based on PiggyBac system, consists of the integration (thanks to a hyperactive transposase PiggyBac -HyPBase) of twelve plasmids that codify up to six different fluorescence proteins (XFs) aim to cytoplasm or nucleus. To target single NG2 or GFAP-progenitor cells, we echanged the CMV-promoter of HyPBase in UbC-StarTrack for NG2 or GFAP-promoter in UbC-(NG2-PB)-StarTrack or UbC-(GFAP-PB)-StarTrack, respectively. After targeting NPCs at either E12, E14, E16 or P0, we performed a clonal analysis of the derived-cell progeny at P30. Data showed that GFAP- and NG2- expressing progenitors produce distinct cell types and whose differentiation potential changes with time and space. Our results provide new data of the lineage cell potential of NG2 and GFAP-progenitors that strengthen the heterogeneity of NPCs during cortical development.

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PS3-10

Microglia gradually acquire their mature phenotype in the developing hippocampus

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Microglia originate from yolk sac progenitors and invade the brain at embryonic stages to progressively become integrated in the parenchyma, presenting a brain-specific phenotype that distinguish them from other tissue macrophages. During the first postnatal weeks of development, microglia go over a period of high transcriptional heterogeneity before their mature phenotype is settled. However, the molecular mechanisms by which microglia identity and function are established and maintained are largely unknown. We hypothesize that microglia morphology and function progressively mature once they enter the brain parenchyma. To test this hypothesis, we focused on the hippocampus because it develops its cellular network during the first postnatal weeks, when microglia heterogeneity is at its peak. We analyzed microglial morphology and phagocytosis efficiency by confocal microscopy, and microglial dynamics by 2-photon microscopy. We found that microglia progressively invaded the hippocampal dentate gyrus from postnatal day 2 (P2) to P10. We are currently exploring two possible routes of colonization: one resembling that of neural precursors, based on the co-localization with the reelin scaffold; and another one related to meningeal macrophages, which decrease over time as microglia increase in the parenchyma. Then, microglia progressively acquired a branched morphology and achieved their highest efficiency of phagocytosis at P14. Hence, they invaded the hippocampus in the first postnatal days, and subsequently acquired their characteristic morphology, dynamics, and mature function. The concurrent maturation of microglia and the hippocampal structure in the first postnatal days suggests the intriguing hypothesis of an active role of the brain environment. Deciphering the microglial maturation program is highly relevant because early changes could be genetically imprinted and lead to long-term functional alterations, which could have an impact in many neurodevelopmental and neurodegenerative disorders.

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PS3-11

The sound of sight: mapping crossmodal circuits of audio-visual connectivity in the mammalian brain.

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In the mammalian neocortex, information corresponding to different sensory modalities is processed separately in specialized cortical areas. Nevertheless, brain regions that process the inputs from different senses are interconnected and provide contextual information to each other, allowing multisensory integration. However, how this integrative and crossmodal network is formed and shaped during development is not well understood.

We have recently reported axonal exuberance as a principal cellular strategy for the establishment of cortical circuits. At the early stages of development, neurons from most areas and layers of the neocortex develop transient projections to ipsi- and contralateral cortical territories. Normally, these exploratory branches are not stabilized. However, in the context of loss of sensory inputs or brain insult in young brains, this early plasticity facilitates the rearrangement of crossmodal canonical connections, resulting in non-canonical circuits. Such might be the case of congenitally blind people, where visual cortices respond strongly to auditory inputs.

To investigate how these associative networks are initially formed and later on refined, we reconstructed audio-visual circuits by combining in-utero electroporation (for anterograde labeling) with stereotaxic injections of the Cholera Toxin Subunit-B (for retrograde labeling) in wild type adult and postnatal mice. We observed that both, primary (V1) and secondary (V2) visual areas, receive inputs from distinct auditory areas. Interestingly, the degree of crossmodal connectivity between these regions changes during postnatal development, being secondary areas more represented in the adult circuit. Furthermore, we noticed that the cortical layers involved in this circuit also differed between stages of development. These findings suggest that the audio-visual network undergoes extensive remodeling during the first weeks of life, highlighting the importance of early axonal plasticity for the acquisition of the final configuration of cortical circuits.

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PS3-12

TREK channels and their physiological role in the intracardiac neurons: focusing on temperature and intracellular acidification

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The intrinsic activity of the intracardiac nervous system is determined by cardiac pacemarkers and is strongly modulated by the sympathetic and parasympathetic branches of the autonomic nervous system. Although general mechanisms controlling cardiac activity have been extensively studied, little is known about the electrical properties and function of parasympathetic neurons in the intracardiac ganglion (ICG).

TREK channels, a subfamily of two-pore domain potassium (K2P) channels, are proteins with a crucial role in maintaining resting membrane potential and controlling excitability, but their function in the ICG remains unclear. In this work we investigated the effect of changes in physiological parameters such as increased temperature and intracellular acidification and how these variations affect to cultured mouse ICG neurons behaviour. First, the presence of TREK channels in the ICG was assessed by RT-qPCR and western-blot analysis. Using electrophysiological patch-clamp technique (perforated-patch), passive and active properties were examined at 24 and 37 °C and before and after cytosolic acidification. In current-clamp experiments, the excitability of ICG neurons was clearly reduced when the temperature was increased from 24 to 37 °C, the neurons resulted hyperpolarized, the action potential firing rate decreased, and some action potential characteristics were also affected. The same phenomenon occurred when the cytosolic pH was diminished. Consistently, in voltage-clamp both physiological temperature and intracellular acidification induced outward currents and an increase in conductance through K+ channels. These currents showed similar characteristics to those driven through TREK-type channels.

Altogether, these results highlight the contribution of TREK channels in establishing neuronal excitability properties at physiological temperature and their role as neuroprotective channels in both temperature and intracellular acidification responses.

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PS3-13

Impaired striatal plasticity and dendritic spine remodeling in the premotor stage of an animal model of progressive parkinsonism

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Parkinson's disease (PD) is characterized by a progressive loss of dopaminergic neurons in the substantia nigra compacta (SNc) and accumulation of α-synuclein (α-syn), which underlies complex functional and structural changes in striatal spiny projection neurons (SPNs). Although a reduction in SPNs dendritic spine density has been reported in either postmortem studies of advanced PD patients or rodent models of parkinsonism, it is unknown if these alterations occur since the onset of the nigrostriatal dopaminergic degeneration. Thus, our aim was to study the temporal sequence of functional and structural changes in striatal dendritic spines. For that purpose, animals were inoculated in the SNc with an adeno-associated viral vector coding for A53T mutated human α-syn (hα-syn) and evaluated at 72h, 1, 2 and 4 weeks post-inoculation (p.i.). Synaptic plasticity by chemical stimulation of LTP (cLTP) in isolated striatal synaptosomes and measurement of striatal dopamine by HPLC were assessed. The analysis of the density and morphology of SPNs dendritic spines was performed by microinjection and high-resolution confocal microscopy. The hα-syn group showed an inhibition of cLTP ($p<0.001$) and a decrease in dopamine content ($p<0.01$) since 72h p.i. even before the presence of hα-syn in the striatum and significant dopaminergic neurodegeneration. These functional alterations are associated with a dendritic spine remodeling, as observed by a significant loss of thin spines, along with an increase in the head volume of thin and mushroom spines. These structural changes occur before the development of parkinsonian motor signs and could represent a compensatory mechanism to enhance the function of existing spines, balancing the observed decrease in spine turnover. Thus, our results indicate dysfunctional neurotransmission by impaired striatal synaptic plasticity since very early time points, leading to dendritic spine remodeling, before the manifestation of motor impairment.

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PS3-14

NMDA RECEPTOR CONTENT OF EXCITATORY SYNAPSES IN THE CA1 REGION OF THE HIPPOCAMPUS IS REDUCED IN P301S MICE

Ms. Rocio Alfaro Ruiz[1], Ms. Carolina Aguado[1], Alejandro Martín-Belmonte[1], Félix Hernández[2], Ana Esther Moreno-Martínez[1], Jesús Avila[2], Yugo Fukazawa, Rafael Lujan[1]

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N-methyl-D-aspartate receptors (NMDARs) are pivotal players in synaptic transmission and plasticity underlying learning and memory. Consequently, synaptic dysfunction of NMDARs has been implicated in the pathophysiology of Alzheimer´s disease (AD). The major structural correlate of the cognitive decline and related symptoms of Alzheimer disease (AD) are mainly attributable to synaptic failure. Given the predominant roles of synaptic NMDA receptors (NMDARs) in excitatory synaptic transmission in the brain, changes in their dynamic regulation have been involved in the pathophysiology of AD. Here we use the P301S tauopathy mouse model to examine possible alterations of GluN1, the obligatory subunit of NMDARs, in neurons that overexpress human tau (P301S mutated gene) in hippocampal neurons, using histoblots and high-resolution immunoelectron microscopic techniques. Histoblots showed that the total amount of NMDARs and their laminar expression pattern in different dendritic layers of the CA1 region of the hippocampus decreased significantly in ten-months-old P301S mice compared to age-matched wild type mice but was unaltered in three-months-old P301S mice. At the ultrastructural level, two synapse populations were examined using SDS-digested freeze-fracture replica labelling in the stratum radiatum in mice of 10 months of age: i) on spines of CA1 pyramidal cells; and ii) on dendritic shafts of CA1 interneurons. P301S mice exhibited a significant reduction of synaptic GluN1 compared with wild-type mice in both pyramidal cells (WT: 616,5 ± 25,2 immunoparticles/µm2; P301S: 392,5 ± 27 immunoparticles/µm2) and interneurons (WT: 541,6 ± 31,6 immunoparticles/µm2; P301S: 353,7 ± 23,1 immunoparticles/µm2) (P<0,0001). Our data demonstrate an age-dependent reduction of synaptic NMDARs in P301S mice. These findings support the notion that the progressive accumulation of phospho-tau is associated with synaptic alteration of NMDARs can take place in the absence of Aβ pathology.

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PS3-15

REDUCTION IN THE DENSITY OF GROUP I MGLU5 RECEPTORS ALONG THE NEURONAL SURFACE OF HIPPOCAMPAL CELLS IN A MOUSE MODEL OF ALZHEIMER´S DISEASE

Ms. Ana Esther Moreno Martínez[1], Alejandro Martín-Belmonte[1], Carolina Aguado[1], Rocío Alfaro-Ruíz[1], Jose Luis Albasanz[2], Mairena Martín[2], Yugo Fukazawa[3], Rafael Luján[1]

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Metabotropic glutamate receptor subtype 5 (mGlu5) is implicated in the pathophysiology of Alzheimer´s disease (AD). However, its alteration at the subcellular level in neurons is still unexplored. Here, we provide a quantitative description on the expression and localisation patterns of mGlu5 in the APP/PS1 model of AD at 12 months of age, combining immunoblots, histoblots and high-resolution immunoelectron microscopic approaches. Immunoblots revealed that the total amount of mGlu5 protein in the hippocampus, in addition to downstream molecules (i.e., Gq/11 and PLCβ1), was similar in both APP/PS1 and age-matched wild type mice. Histoblots revealed that mGlu5 expression in the brain and its laminar expression in the hippocampus was also unaltered. However, the ultrastructural techniques SDS-FRL and pre-embedding immunogold, demonstrated that the subcellular localisation of mGlu5 was significantly reduced along the neuronal surface of hippocampal principal cells, including CA1 pyramidal cells and DG granule cells, in APP/PS1 mice at 12 months of age. The decrease in the surface localisation of mGlu5 was accompanied by an increase in its frequency at cytoplasmic sites in the two neuronal populations. Together, these data demonstrate for the first time a redistribution of mGlu5 from the plasma membrane to intracellular sites in different principal cells of the hippocampus in APP/PS1 mice, suggesting an alteration of the excitability and synaptic transmission that could contribute to the cognitive dysfunctions in this AD animal model.

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PS3-16

Trans-synaptic effects after inducing long-term potentiation in the hippocampal circuit

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Long-term potentiation (LTP) evoked by high frequency stimulation (HFS) is a very well-known experimental procedure that shares certain mechanisms with learning and memory processes. LTP is a typical example of synaptic plasticity, which appears after applying an HFS train to the afferent pathway of a CNS synapse. Basically, it consists in an increase of the synaptic response to a control stimulus following the presentation of the HFS train. This technique is studied mostly in the hippocampus due to its high susceptibility to LTP induction and its laminar nature that allows the study of synapses with different ultrastructural dispositions. Although most of preceding studies have been performed in vitro, we have developed a new experimental approach to carry out these experiments in behaving animals. The main goal of this study was to confirm that there are synaptic changes in strength not only in the synapse where LTP is induced, but also in those post-synaptic to it. We studied field excitatory post-synaptic potentials (fEPSP) evoked in five hippocampal synapses, located in both ipsi- and contralateral hemispheres (PP-CA1i, PP-CA3i, PP-CA1c, CA3-CA1i, and CA3-CA1c). HFS was presented to the perforant pathway (PP). Animals were prepared for chronic recordings in the mentioned synapses following procedures described elsewhere (Gruart et al., J. Neurosci., 2006). We have characterized input/output curves, paired pulse facilitation (PPF) and LTP of these synapses. We also performed depth-profile recordings, which showed differences in the synapses' latency. Data from input/output curves and PPF proved that the five studied synapses have similar basic properties, which makes their later comparison easier for subsequent analysis. Importantly, regarding HFS of the PP, we observed the presence of significant LTP both at the CA3-CA1c and PP-CA1c synapses, lasting at least two hours in the first day of recording. In conclusion, these results indicate that LTP can be evoked at synapses located far away from the stimulated afferent pathways.

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PS3-17

Modulation of the presynaptic translatome by astrocytic extracellular vesicles in Alzheimer's Disease

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Neurons are highly polarized cells with an asymmetric morphology, thus implying an asymmetric distribution of proteins. Protein synthesis is vital to guarantee the correct neuronal function. Under physiological conditions, proteins need to be appropriately sorted to the target cellular compartment where they elicit their function. Noteworthy, protein synthesis is not always carried out by the classical translation pathway, in which proteins are synthesized in the rough endoplasmic reticulum and after maturation, proteins are transported to the target compartment. Protein translation can also be executed by another way based on the delivery of the mRNA to the target site, where mRNAs will be locally translated into proteins. This process is known as local protein synthesis.

Neuronal local translation allows for a faster reaction of neural processes in response to environmental cues and contributes to the maintenance of axonal and dendritic homeostasis. In the Peripheral Nervous System, it has been described that extracellular vesicles (EVs) secreted by Schwann cells are capable of contributing to local protein synthesis and regenerate injured nerves. Nevertheless, it is so far unclear whether glial cells are involved in local protein synthesis.

Recent evidence show that in Alzheimer´s disease (AD) pathology local protein synthesis is involved in the transmission of β-amyloid pathology from the axons to the soma. In this way, the retrograde transport of proteins synthesized in the axon in response to amyloid peptide leads to pathological transcriptional changes that contribute to neurodegeneration in AD. Furthermore, previous results of our research group have found evidences supporting that EVs secreted in presence of astrocytes modifies the levels of translation in axons of the Central Nervous System in vitro, both under physiological and AD conditions. Based on these facts, the working hypothesis is that astrocytes contribute to presynaptic translatome through the transfer of EVs in physiological and AD conditions.

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PS3-18

Contribution of astrocyte extracellular vesicles to local translation in neurons

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Local protein synthesis is a conserved mechanism by which mRNAs are localized to the cell periphery and proteins are synthesized at target sites. Local translation is especially relevant in polarized cells like neurons so that neurites can rapidly react to changes in their environment. For instance, the exposure of isolated axons to β-amyloid oligomers (Aβo), central to Alzheimer's disease, induces local protein synthesis and mediates neurodegeneration contributing to the disease. However, axons are not isolated in the nervous system but surrounded by other compartments or non-neuronal cells. Our laboratory is interested in the contribution of glial cells to local translation in neurons. Others have reported that extracellular vesicles (EVs) secreted by astrocytes are involved in the regulation of different neuronal functions. Based on these data, we hypothesize that astrocyte-derived EVs are delivered to neurons to modulate local protein synthesis in physiological and Aβo- induced conditions.

To assess the relevance of astrocytes in neurons local proteome, we isolated somata and neurites from primary cortico-hippocampal neurons cultured in Boyden chambers in absence/presence of astrocytes and analysed the extracted proteins by LC-MS/MS. Results show that the presence of astrocytes in control conditions changes the neuritic proteome. Gene Ontology analyses show that proteins significantly regulated in presence of astrocytes vs their absence are mainly involved in RNA binding, processing and translation. In Aβo-induced conditions, astrocytes also change neuritic proteins compared to only- neuron cultures, with translation-involved proteins among them. To determine whether these proteins are locally synthesized in neurites, we have selected 176 and are analysing their corresponding transcripts in somata and neurites.

We have also assessed if EVs are directly involved in translation regulation. Isolated EVs from neuron-astrocyte cultures increase translation levels in neurites, suggesting that EVs are relevant for local protein synthesis in neurons. We are deeply studying EVs by LC-MS/MS to search for translation regulators.

Altogether, our data provide a new mechanism of local translation regulation in which astrocyte-derived EVs could play an important role.

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PS3-19

Comparative effect of Glutamatergic Receptors Agonists N-Methyl-D-Aspartate and Kainate on Mouse Inner Retinal Cells

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Purpose: Due to the heterogeneous sensitivity of the different retinal neurons to glutamate agonists, our objective is to compare the effect of two glutamate agonists, N-methyl D-aspartate (NMDA) and kainate (KA) on inner retinal cells. Recently, our group has developed a mouse model of inner retina degeneration induced by a combined intravitreal injection of those two glutamatergic agonists. Methods: C57BL6/J mice were intravitreally injected into the right eye with 1µL of PBS containing NMDA 10 mM or KA 3 mM (1µL PBS was inoculated into the contralateral eye). The effect on retinal function was evaluated post-injection by optomotor test and electroretinographic (ERG) recording. The structural retinal damage was assessed by immunohistochemical labelling of retinal cells on retinal sections. Results: Intraocular injection of NMDA/KA (10/3 mM) induces the abolition of optomotor response and a strong decrease of ERG b-wave at one-week post-treatment, but does not show any functional nor structural alterations in photoreceptors. Both excitotoxic agents, when injected independently, caused a complete loss of optomotor response just 3 days post-injection. The sole KA (3 mM) treatment produced the loss of b-wave ERG components, both in scotopic and photopic conditions. By contrast, NMDA-treated eyes preserved these ERG components, but a marked decrease in their amplitude was observed. Nonetheless, no significant changes on the “a” wave amplitude were found after the injection of both agents. Immunohistochemical labeling showed no effects of NMDA nor KA on the outer nuclear layer, but a moderate damage on the inner retinal layers in NMDA-injected eyes, and a deleterious effect in KA-injected eyes. Conclusion: Retinal damage induced by KA shows a stronger effect than NMDA. However, differences observed between NMDA and KA injection could be caused by the different sensitivity of the retinal neurons, maintaining the possibility of inducing a synergic interaction with lower concentration of KA.

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PS3-20

M1 and M2 muscarinic receptors coordinately regulate the exocytotic proteins through PKC and PKA at the adult neuromuscular junction.

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Synapses use plastic mechanisms to adjust the strength of the neurotransmitter release to any situation. At the neuromuscular junction (NMJ), muscarinic acetylcholine receptors (mAChR) participate in synaptic plasticity as presynaptic autoreceptors sensing and controlling the release of acetylcholine (ACh). M_1 and M_2 subtypes increase and decrease, respectively, neurotransmitter release. M_2 involves PKA and M_1 PKC. Several PKC and PKA targets contribute to the synaptic vesicle exocytosis and their coordination is fundamental to achieve the extraordinary speed, precision and plasticity of neurotransmission although the molecular signaling regulation is unknown. Therefore, the present study is aimed to know how M_1 and M_2 mAChRs regulate (1) their own and mutual expression, (2) PKA subunits dynamics and activity, (3) PDK1 activity, (4) nPKCε and cPKCβI, and (5) Munc18-1, MARCKS and SNAP-25 phosphorylation. We performed immunohistochemistry and confocal techniques to evidence the presynaptic location of the regulated molecules. Specific inhibitory reagents were used to block M_1 and M_2 mAChR, nPKCε, cPKCβI, PKA and PDK1 activity.
Main results obtained from Western blot, co-immunoprecipation and subcellular fractionation experiments showed that: (1) M_2 downregulates M_1. (2) M_2 inhibits PKA activity by downregulating Cβ subunit, upregulating RIIα/β and liberating RIβ and RIIα to the cytosol reducing the phosphorylation of SNAP-25 on Thr-138 and CREB. M_1 signaling opposes to M_2 by recruiting R subunits to the membrane. (3) M_1 and M_2 mAChR activate the master kinase PDK1, which promotes the priming of the presynaptic PKCβI and PKCε isoforms. (4)M_1 recruits both primed-PKCs to the membrane and promotes (5) Munc18-1, SNAP-25 and MARCKS phosphorylation. In contrast, M_2 downregulates PKCε through a PKA-dependent pathway, which inhibits Munc18-1 synthesis and PKC-phosphorylation.
The results demonstrate the coordinate and dependent action of the M_1 and M_2 mAChRs on ACh release SNARE-SM mechanism involving PKC and PKA to regulate neurotransmission and guide towards potential therapeutic targets.

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PS3-21

EFFECTS OF TRANSCRANIAL DIRECT-CURRENT STIMULATION (tDCS) ON THE FIELD POTENTIAL INDUCED BY PHOTOSTIMULATION OF GLUTAMATERGIC CELLS IN SOMATOSENSORY CORTEX

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Transcranial Direct-Current Stimulation (tDCS) is a non-invasive brain stimulation technique that can influence brain excitability. Although previous studies have demonstrated the modulatory effects of tDCS on cortical activity in different brain regions, the mechanisms underlying its physiological effects are not fully understood. It has been hypothesized that different neuronal populations diversely response to exogenous electric field according to their morphology and orientation. In this study, we use an optogenetic approach to know about the impact of the electric field on different neuronal groups.

For that, wild-type mice were injected with an adeno-associated virus containing the gene encoding ChR2 preceded by the CAMKII promoter to selectively photostimulate glutamatergic neurons in the primary somatosensory cortex (S1). Three weeks after virus infection, mice were prepared for chronic recording of LFPs in S1 during photostimulation and simultaneous tDCS in head-restrained condition.

The evoked field potentials in response to blue light was characterized for different light duration and intensity by using optrodes. To describe the impact of tDCS on glutamatergic neuronal population, short pulses (15 s, including 5 s ramp up and 5 s ramp down) of transcranial currents were delivered over S1 at different intensities and polarities (±50, ±100, ±150 and ±200 μA). An electrical stimulus (0.2 ms, <0.2 mA) was applied to whisker pad 2 s before photostimulation as a control during tDCS protocol.

The induced field potentials in response to blue light were proved to be directly dependent on both light exposure and light intensity. During the application of anodal tDCS, we observed an increase in the amplitude field potentials induced by whisker and optogenetic stimulation whereas cathodal tDCS decreased it.

These results prove that optogenetics is a valid and effective technique to study the effects of tDCS on distinct neuronal populations, a fundamental knowledge to understand and optimize future clinical applications.

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PS3-22

Effect of Sei and Fin whale Müller glia in the survival and neurite growth of RGCs in vitro.

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Müller cells are crucial in retinal homeostasis. In zebrafish and lower vertebrates, spontaneous retinal regeneration was observed. In the mammalian retina, there is no such evidence. However, recent studies have been demonstrated that Müller cells promote the survival and the neurite outgrowth of RGCs in vitro. Here, the effect of Müller cells from two of the largest mammals in the world, Fin and Sei whales, was analyzed on RGCs survival and neurite outgrowth.

The retinas of beached Balaenoptera physalus and Balaenoptera borealis whales, 24h post-mortem, were studied. Cultures of Müller cells were grown and, once whale Müller cells reached confluence, adult rat RGCs were seeded on Müller cells. The cells were cultured during six days. The number and length of the neurites of the RGCs were quantified. The conditioned media (CM) from whale Müller cells was analysed by mass spectrometry to identify and quantify proteins. Results were compared to the CM from pig Müller cells. NELL2, SEMA3F, CD56, NRCAM, OGN and PEDF were selected as candidate factors to promote neurite outgrowth and tested in pure rat RGCs cultures.

RGCs survival increased 60% when cultured with whale Müller cells. The length of the neurites (>200µm) increased 90% and the length of the longest neurites (>1000µm) increased more than 500%. Proteomic analysis from whale Müller cells CM showed that the function of the 10% of the most represented proteins detected were related to neurite outgrowth, compared to only 2% of the proteins in pig CM. The selected proteins induced an increase in the percentage of RGCs with long neurites (>200µm) and an increase of 200% in RGCs with very long neurites (>1000µm).

Whale Müller cells increase RGCs neurite growth, suggesting that whale Müller cells secrete a combination of neurotrophic factors promoting regeneration of RGCs. Besides, the selected proteins from the CM increase neurite outgrowth, confirming the capacity of the factors secreted by whale Müller cells to regenerate RGCs.

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PS3-23

Chemogenetic stimulation of mature oligodendrocytes drives myelin-axon metabolic coupling and prevents axonal damage

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Oligodendrocytes make myelin and support axons metabolically with lactate. Experience and neuronal activity can induce dynamic changes in myelination during development and in adult life, suggesting a new form of plasticity to adapt brain function to environmental stimuli. Myelin remodeling is driven mainly by newly-formed oligodendrocytes from precursors cells. However, the role of mature oligodendrocytes in plastic changes of myelin is practically unknown. We have generated transgenic mice, using the CreERT2-lox technology, overexpressing the DREADD receptor hM3Dq under the PLP promoter, specific of mature oligodendrocytes. Chronic stimulation of hM3Dq receptors induced an increase in myelination of axons in cerebral cortex and corpus callosum, and consequently, an increase in axonal conduction velocity of interhemispheric callosal connections. Importantly, acute stimulation of hM3Dq+ activates metabolism in oligodendrocytes. We detected an increase in glycolytic rate and in lactate production and release. Moreover, these higher metabolic coupling between oligodendrocytes and axons maintained axonal function under high frequency stimulation and prevented axonal damage secondary to oxygen glucose deprivation. We then tested the impact of mature oligodendrocytes stimulation to promote remyelination and protect axons in demyelinating disease models. Preliminary data show that chemogenetic oligodendrocyte stimulation ameliorates motor symptoms of mice with experimental autoimmune encephalomyelitis, a model of multiple sclerosis. Taken together, these findings indicate that this chemogenetic mouse line is a very useful tool to elucidate the contribution of mature oligodendrocytes to myelin remodeling in physiological and pathological conditions, and reveals a novel role of myelin-axon lactate shuttle in axonal protection.

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PS3-24

Dopamine receptors in oligodendroglia

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Several neurotransmitters have been shown to act on oligodendrocytes or their precursors but the function of this action is unknown. Neurotransmitter agonism or antagonism influences the development and differentiation of oligodendroglia and, as a result, the myelination process. Dopamine receptors have been reported to exist in oligodendrocyte precursor cells (OPCs) but evidences about their function are scarce. We have generated enriched oligodendroglia cultures from rat cortical neural progenitor cells, followed by O4+ cell sorting, as well as by direct conversion from adipose tissue stromal cells overexpressing Sox10 + Olig2 + Zfp536 (SOZ-induced oligodendroglia). RT-qPCR analysis showed that both D1-type (DRD1 and DRD5) and D2-type (mainly, DRD2) mRNA are expressed in brain-derived OPCs and that differentiation by growth factor (EGF, bFGF and PDGF-AA) withdrawal and T3 addition changed to a predominantly D1-type expression. SOZ-induced oligodendroglia showed a similar expression pattern of dopaminergic receptors. Functionality of these receptors was assayed by measurements of cAMP levels in response to dopaminergic agonists and antagonists. Immunofluorescence (O4 and NG2) analyses show that dopaminergic agonists of both types influence the proliferation and morphological maturation of oligodendroglia. These results support that dopamine inhibits oligodendrocyte differentiation and myelination. Excess of dopamine during the formation of neuronal tracts might have a negative effect on their myelination and thus impair their functionality. An impaired myelination of some corticofugal tracts due to a hyperdopaminergic environment at critical periods of brain development might be in the basis of neuropsychiatric disorders like schizophrenia.

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PS3-25

Astrocytic Network Heterogeneity in the Nucleus Accumbens

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Astrocytes have been traditionally studied as a homogeneous group, however, recent research has started to evidence their heterogeneity between different brain areas and within the same region. Our hypothesis is that specialized astrocyte subsets are responsible for the modulation of specific neuronal circuits. In the NAc converge different glutamatergic signals coming primarily from the medial prefrontal cortex (mPFC), basolateral amygdala (Amyg), and ventral hippocampus (vHip), providing us the perfect structure to study the presence of specialized astrocytic networks.

In this work, we analyze whether astrocytes establish segregated populations in the NAc with intrinsic properties and functional consequences for the circuit. To this end, we have used optogenetic manipulations to perform afferent-specific synaptic stimulation to the NAc, combined with a new adapted technique (CaMPARIGFAP, calcium-modulated photoactivatable ratiometric integrator under GFAP promoter) to specifically dissect the active astrocyte circuits with spatio-temporal precision.

We demonstrate that NAc astrocytes show pathway-specific interactions with the glutamatergic afferents coming from the mPFC, Amyg, and vHip, and that this activity unexpectedly does not correlate with glutamatergic innervation patterns, suggesting astrocytic connectivity, i.e. activation of a precise astrocytic population in response to specific glutamatergic inputs. Moreover, the activation of these defined spatial astrocytic networks are not influenced by alterations in astrocyte density or by uneven expression of mGluR5. Finally, we show that different sub-populations of astrocytes in both NAc regions receive and integrate signals arising from all the excitatory afferents.

This work reveals astrocytic functional heterogeneity in the NAc regarding glutamatergic signaling, showing pathway-specific astrocytic responses mediated by mGluR5. Also, all these observations provide a potential explanation for comprehension of how NAc integrates information from multiple glutamatergic regions.

PS3-26

MONITORING OF ABERRANT NEUROGENESIS IN HIPPOCAMPUS DURING IN VITRO EPILEPTOGENESIS

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Epilepsy is among the most common and severe neurological disorders, yet epileptogenesis is poorly understood. The epileptic focus in temporal lobe epilepsy is frequently found in the hippocampus, where it causes sclerosis and aberrant neurogenesis in the dentate gyrus. Our goal here is to understand what alterations take place in the neurogenic niche during epileptogenesis.

Organotypic hippocampal cultures (OTCs) are a widely used in vitro model of temporal lobe epilepsy, and offers unique optical access to the hippocampal circuit over days and weeks in vitro. We have successfully established a model of OTCs and retro viral vector-based cell labeling of newborn neurons in order to assess aberrant neurogenesis in epileptic conditions induced by addition of the GABA-A receptor antagonist picrotoxin (PTX). We have verified that the epileptic environment reduces newborn neuron density, diminishes their morphological complexity and increases cell death.

Through the addition of cerium nanoparticles (CeO2NPs), which harness strong anti-oxidative stress action, we have reversed cell death and recovered newborn neuron density. The reduction in morphological complexity of newborn neurons induced by PTX was however worsened by CeO2NPs.

We have also observed that in epileptic conditions there is a reduction in GABA cell density, and specifically in GABAergic newborn neurons. Our hypothesis is that newborn neurons need GABA input to be GABAergic. By adding tetrodotoxin, which mimics the effect of increasing GABA input in the slices, we observed that the GABAergic newborn neuron percentage was recovered. This proves that blocking GABA-A receptors is not the reason why there are fewer GABAergic newborn neurons in epileptic conditions, but the activity that occurs after this blocking, which favors hyperexcitation. Therefore, we can conclude that GABAergic newborn neuron survival does not depend on GABA input, increasing our interest in trying to assess what occurs during the GABAergic period.

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PS3-27

RNA localisation and local translation in microglial peripheral processes

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Local RNA translation allows the cells to respond fast and efficiently to environmental stimuli. Local translation is especially important in highly polarized cells, such as neurons, because it provides axons and dendrites a means for an accurate response to fast environmental changes. Although most of the work on local protein synthesis in brain cells has been performed in neurons, we now know this phenomenon is not restricted to these cell types. For instance, local translation has been described in peripheral astrocytic processes. In astrocytes local protein synthesis is essential for astrocytes to be involved in synapsis (Sakers et al., 2017). Furthermore, in oligodendrocytes it has been seen that MBP is translated locally in neurodegenerative conditions and during differentiation (Quintela-Lopez et al., 2019). Only recently localized translation in microglia has been established (Vasek et al., 2021), however its role in the pathophysiology of the brain has not been addressed. We propose that local translation in microglia plays fundamental roles in brain function and dysfunction.

We have exposed microglia to different stimuli, like LPS, ATP, Aβ and MCSF, and analysed how they affect local translation in microglial peripheral processes. LPS is the only stimulus inducing changes in local protein synthesis, as well as inducing changes in global RNA localization at the interface between microglial lamellae and filopodia (the leading edge). Additionally, Actb transcripts are increased in microglial lamellae and filopodia in response to LPS with LPS.

So far, our results indicate that local protein synthesis might be required for the inflammatory response in microglia cells. We are currently analysing localized translation of Actb and other transcripts involved in cell polarity and cytoskeletal rearrangements using puromycilation combined with proximity ligation assay (Puro-PLA).

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PS3-28

Role of GABAA and AMPA receptors in the generation and propagation of epileptiform activity in the cingulate cortex of a mouse model of lissencephaly.

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The mutant mouse Lis1/sLis1 is a model of mild human lissencephaly that is very useful to study the role of the gene LIS1 in the pathophysiological mechanisms related to this disease. A prominent clinical feature of lissencephaly is the presence of intense epileptic seizures, and we have studies the pharmacology of the generation of epileptiform electrophysiological activity in the anterior cingulate cortex (ACC) of the Lis1/sLis1 mouse. The experiments were done using coronal brain slices and extracellular recording of epileptiform discharges (ED) in layer 2/3 of the ACC; the ED were evoked by electrical stimuli applied to layer 1 and in the presence of bicuculline (a blocker of GABAA receptors).

The sensitivity to bicuculline (tested at concentrations of 0.1–20 microM) of then generation of ED was similar in WT and Lis1/sLis1 ACC. The bicuculline D50 was 3.26±1.16 microM, n=11 and 2.95±1.22 microM, n=9 (WT and Lis1/sLis1 respectively); the D50 was measured from the dose-response relationship between the concentration of bicuculline and the size of the ED. To explore the role of AMPA receptors in the generation and propagation of ED we tested the effects of AMPA receptors antagonists. CNQX (1microM; a blocker of AMPA/kainate receptors) produced an increase of the latency of ED that was significantly larger in WT than in Lis1/sLis1 slices (WT: 15.35±2.67ms, n=11; Lis1/sLis1: 9.40±4.02ms, n=8; p=0.029 RankSumTest). GYKI53655 (2microM; a selective AMPA receptor blocker) produced a dose-dependent increase of the latency that was larger in WT than in Lis1/sLis1 (WT: 39.03±13.27%, n=4; Lis1/sLis1: 3.27±3.88%, n=6; p=0.038, RankSumTest), and a similar decrease of the size of ED (WT: 32.12±20.8%, n=4; Lis1/sLis1: 31.76±15.4±3.88%, n=6; n.s.)

These data suggest that in Lis1/sLis1 ACC the sensitivity of the generation of ED was normal, but there were abnormalities in AMPA receptors.

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PS3-29

Expression of c-Fos in the vomeronasal amygdala and lateral entorhinal cortex of female mice induced by male pheromonal signals.

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In mice, individual recognition is based on the major urinary proteins present in urine, detected by the vomeronasal system. These signals are integrated into the posteromedial cortical amygdala (PMCo). The PMCo projects to the dorsal lateral entorhinal cortex (dLEnt), which also receives olfactory inputs from the main olfactory bulb and piriform cortex. Thus, vomeronasal information from the PMCo may converge in the dLEnt with olfactory information, from where it would be relayed to the dorsal hippocampal CA1 (dCA1), reaching the hippocampal memory system as a complex chemosensory input. To assess the effect of urine stimuli on the c-Fos activity of the PMCo-dLEnt-dCA1 circuit, we tested the preference of CD1 female mice to investigate male urine (n=5) or a control odorant (citralva; n=5) located in a particular corner of the cage during a 90 minutes test. Exploratory behavior was quantified with DeepLabCut, a software based on deep learning methods, and subsequent data were processed with self-written Python code. This analysis showed that male urine induced a significantly higher exploration than citralva. The immunofluorescent detection of c-Fos revealed a significantly higher expression in the PMCo and dLEnt in mice exploring urine. Since neurons in dLEnt projecting to dCA1 are reelin-positive, we performed a double immunofluorescence detection of c-Fos and reelin. The results showed a significantly higher number of c-Fos/reelin-positive neurons in the experimental group and a positive correlation with exploration time. In contrast, the number of c-Fos-positive cells in dCA1 did not differ between mice exploring urine or the neutral odorant. The results suggest that vomeronasal information encoding individual identity reaches the hippocampal memory system through the dLEnt. The lack of differential c-Fos expression in CA1 may indicate that citralva is also inducing memory formation, but following a different path.

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PS3-30

LACK OF AVERSIVE BEHAVIOR IN FEMALE MICE EXPOSED TO PREDATOR ODORS

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The avoidance of danger and the detection of possible threats to the survival are behaviours present in all animal organisms. In fact, detecting and avoiding danger has probably been a strong evolutionary pressure for the development of sensory systems allowing this survival behaviour.

In animals, detecting the presence of a predator nearby and avoiding the territories with abundant predator signals is an important advantage for the survival of prey. In many mammals this detection is based on chemical cues. The chemical cues of other species that signal the presence of a predator are called kairomones. In Mus musculus, previous studies have reported possible kairomones for a variety of natural predators as foxes, cats or rats.

In this work we report a series of experiments with the objective of investigating the aversive or avoidance behaviour of mice against some chemical cues obtained from cats (cotton impregnated with saliva; cotton impregnated with secretions of the perianal gland of a cat; and cat bedding) and trimethylpirazine 13, a molecule found in wolf urine that has been reported to elicit avoidance behaviour in mice. The predator-derived stimuli were presented in preference tests against the same type of substrate containing the stimuli (cotton, bedding or filter paper), either clean of with saline.

Our results show no statistical difference in the time spent investigating the neutral and the predator odours used, and we observed no sign of avoidance or freezing behaviour. We conclude that the presence of these chemical cues is not sufficient to elicit avoidance or defensive behaviours. We hypothesize that, for the occurrence of this species-typical behaviours, it might be necessary the co-occurrence of other factors, related with the context, the internal state of the animal and the chemical characteristics of the stimuli.

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PS3-31

The amygdalo-hippocampal pathway: the first step to the who component of the episodic memory

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One of the most complex issues in episodic memory is how the different types of information that contribute to an event are integrated. Within the hierarchy underlying memory formation, spatial (where) and temporal (when) memory must be integrated with social (who) memory to compose a complete episodic memory. Anatomical data suggest that vomeronasal information (encoding individual identity in mice) reaches the hippocampus indirectly via the lateral entorhinal cortex.
Since the primary vomeronasal cortex is the posteromedial cortical amygdala (PMCo), we hypothesize that it constitutes the first step of a putative pathway for integrating pheromonal signals into hippocampal-dependent memory in rodents. To test this hypothesis, simultaneous local field potentials (LFPs) in the PMCo and CA1 were recorded in awake head-fixed mice while exploring a virtual environment associated with olfactory and vomeronasal stimuli. The system consisted of testing corridors in which mice can navigate using a running wheel in a one-dimensional space, forcing exploration of experimentally controlled stimuli.
Active exploration was highly correlated with theta activity (5-12 Hz), not only in the hippocampal LFP but also in the PMCo. Consequently, high-coherence oscillations of both signals evidenced theta epochs, indicating plausible oscillatory theta co-activity. Furthermore, causal epochs could be detected during these active periods. A salient feature of this theta profile was its co-occurrence with gamma waves (30-200 Hz), a cross-frequency interaction related with phase encoding related to hippocampal formation.
We focused our analysis on the different spectral signatures profiled by gamma waves embedded in theta cycles. A similar set of five theta-nested spectral components was present in both PMCo and CA1 when vomeronasal signals were present, again suggesting coupled neural processing in the two areas, related to the incorporation of conspecific information into hippocampal memory

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PS3-32

Input-output relationships of the posterior intralaminar thalamic nuclei in the mouse

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The posterior intralaminar thalamic nuclei (PIN = Parafascicular nucleus + Ethmoid-Limitans nucleus) are a massive source of subcortical excitatory inputs to the striatum. Moreover, PIN neuron axons simultaneously innervate the cerebral cortex as well; however, the functional logic of this divergent projection is currently unclear. Likewise, sources of cortical and subcortical input to PIN neurons remain poorly defined.

Here, using wild-type adult C57BL/6 male mice as experimental subjects, we set out to a) map PIN afferents; b) sort out the relationship between PIN subregions and the cortical + striatal territories targeted by their projections; and c) elucidate the existence of differences in axon varicosity morphology/size in PIN axons in specific cortical layers or areas and/or striatal (matrix/striosome) domains. We made selective microinjections of biotin dextran amine (BDA) or a mixture of BDA and Cholera Toxin B Subunit in different PIN subdomains to visualize their efferent and afferent projections. We applied immunolabeling against μ-opioid receptor or glycine transporter 2, or histochemical stainings as thionin, cytochrome oxidase or acetylcholinesterase to delineate relevant brain territories.

Our data show that the mouse PIN receive massive inputs from, among other structures, motor cortex layer 5 cells and the multimodal intermediate/deep layers of the superior colliculus. Cortical layer 6 projections are robust as well. In turn, PIN projections to striatum and cortex are topographically organized, and the same PIN neurons innervate somatotopically-congruent regions in both structures. Axonal varicosity sizes vary depending on the target structure and the origin of the axons within the various PIN subregions. These observations suggest that the divergent PIN output to the striatum and the cerebral cortex is segregated into parallel, somatopically-related subcircuits.

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PS3-33

Prefrontal-hippocampal circuit alterations and rescue in a mouse model of schizophrenia

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Disruption of neural synchrony and spatio-temporal communication in brain circuits involving the prefrontal cortex (PFC) and the hippocampus (HPC) has been suggested to be a hallmark characteristic of neuropsychiatric disorders such as schizophrenia (SCZ). SCZ patients show positive symptoms that can be effectively managed with antipsychotic drugs (ADPs). However, negative symptoms and cognitive deficits are inadequately treated. Therefore, a better understanding of the prefrontal-hippocampal neural basis of these symptoms is essential for the development of new treatments. We investigated the alterations of prefrontal-hippocampal circuits in the acute (PCP) and subchronic (sPCP) phencyclidine mouse model of SCZ, that assess the positive and cognitive symptoms of SCZ, respectively, and examined the recovery by typical and atypical APDs. First, we recorded neural activity in the PFC and HPC of C57BL/6J mice treated acutely with PCP alone or PCP followed by one APD (risperidone, clozapine or haloperidol). Acute PCP produced hypersynchronization and disrupted communication of prefrontal-hippocampal pathways that were efficiently recovered by ADPs. In another set of mice, we recorded the activity before and after administration of sPCP during an open field exploration, three auditory tasks and the novel object recognition test that assesses working memory and long-term memory abilities. We also investigated behavioral and neurophysiological rescue by a 14-day risperidone treatment. sPCP-treated mice showed abnormal gamma oscillations (30-100 Hz) and theta-gamma cross-frequency coupling during rest. Notably, auditory perception, working memory and long-term memory were profoundly impaired in sPCP-treated mice and were accompanied by disrupted prefrontal-hippocampal functional connectivity. Both, memory deficits and functional connectivity were rescued by risperidone. Our findings suggest that abnormal prefrontal-hippocampal neurodynamics may contribute to the neural mechanisms of SCZ and some of these alterations can be rescued by ADPs.

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PS3-35

SPATIAL PERIODIC FIRING IN THE SUBICULUM OF MICE

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Spatial cognition relies on a complex circuitry in which the hippocampal formation seems to be crucial. The subiculum is a region located at the core of this circuit, it receives inputs from grid cells located in the medial entorhinal cortex (MEC) and place cells from the CA1 area of the hippocampus. It integrates input from these two relevant spatial information sources and mediates the output from the hippocampus to cortical and sub-cortical areas also involved in spatial coding. Despite the potential relevance of the subiculum, its role in memory and spatial coding is still poorly understood. Previous work described a very heterogeneous population of spatial neurons in the subiculum, with evidence of its role in coding the geometry of the environment and in spatial navigation in darkness. However, its role in spatial coding remains to be unveiled. With the aim of understanding further the properties of spatial coding in the subiculum, we implanted mice with microdrives mounting tetrodes and multisite electrodes aiming at the CA1 and subicular area, and recorded neuronal activity across different behavioral paradigms. Our results indicate that place cells in CA1 present higher spatial resolution and sharper firing fields than those of subicular neurons. Also, place cells in the CA1 area seem to be differentially modulated by the local field potential. Interestingly, we found pyramidal neurons in the subiculum with periodic firing, the first evidence of this type of regular firing in subicular pyramidal neurons.

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PS3-36

Cell-type specific wiring between ventroposterior thalamic nucleus neurons and somatosensory cortices

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The ventral posterior nucleus (VP) of the thalamus is the relay station for somatic sensory inputs to the cortex. Thalamocortical axons carrying mechanoceptive information from mystacial vibrissae follicles to the primary somatosensory area (S1) in rodents are a key model in sensory systems neuroscience. In contrast other thalamocortical pathways originated in rodent VP have received much less attention, to the point that even their cellular wiring remains poorly defined. Here, using micropopulation and single cell-axon labeling, systematically charted and analyzed structural differences between the various output circuits established between VP cells and the cerebral cortex.

Our data show that, while, as expected, axons coming from populations in rostrodorsal VPM target area S1 upper layer 4 (L4) in focal, point-to-point fashion, the cells in a large ventrocaudal domain of VPM target instead the second somatosensory area (S2) L4, also in point-to-point fashion. Besides, cells from a ventrolateral VPM domain target S1, arborize in layers 2-3 and deep L4, avoiding “barrel” cores. Cells in the lateral ventroposterior nucleus (VPL) target S1 and S2 simultaneously, often via collaterals of the same axons. Reconstruction of the complete axonal tree of transfected single cells (Neurolucida) reveals quantitative differences in the distribution of axonal arborizations in different areas and layers. Our results indicate the existence of several parallel thalamocortical pathways between VP and somatosensory cortices, depending each of a specific projection neuron subtype.

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PS3-38

Neural mechanisms of serial dependence across visual hemifields and bilateral prefrontal cortex

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It has been shown that previously perceived working memory (WM) items have an effect on current WM reports. This effect is called serial dependence and has been shown to rely on the interaction of active neural representations and long-lasting activity-silent mechanisms in prefrontal cortex (PFC) [Barbosa, Stein et al., 2020]. Furthermore, it has been shown that WM representations are more frequent for contralateral than for ipsilateral memorized locations in PFC [Funahashi et al., 1989] and that active representations transfer between hemispheres when midline-crossing saccades occur in the delay [Brincat et al., 2021]. This indicates the consistent specialization of each hemisphere for the corresponding visual hemifield in WM. However, serial dependence challenges this view as it is unclear how it can emerge when consecutive stimuli appear in different hemifields, which engage independent neural substrates. Here, we investigate the transfer of serial dependence between visual hemifields and the associated prefrontal correlates across hemispheres, in order to shed light on the mechanisms of integration of lateralized WM storage. We collected simultaneous multi-unit recordings in bilateral PFC of 3 monkeys performing an oculomotor visuospatial delayed response task. We analyzed behavioral responses, and population coding in neural data in relation to serial dependence. Decoding from neural traces was used to predict behavioral biases of the monkeys for separate hemifields and hemispheres. We found that serial dependence of stimuli presented across hemifields was diminished in comparison to trials within the same hemifield. Furthermore, the decoded neural traces between hemispheres reflected these differences. We conclude that small biases towards previous memories in WM are partly supported by lateralized mechanisms. This shows an incomplete continuity of serial dependence in WM, which is in line with the activity-silent theory for serial dependence.

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PS3-39

Neuronal activity reflecting sensory and behavioural variables in the mouse somatosensory and posterior parietal cortex

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Real-world signals such as communication sequences unfold over time with a characteristic temporal structure. Recognizing temporally ordered patterns is key to survival. To explore how cortical neuronal activity underpins this capacity, we recently developed a task in which mice distinguished between tactile 'word' sequences constructed from distinct vibrations delivered to the whiskers, assembled in different orders. We combined task performance with two-photon imaging and optogenetics.

Animals licked to report the presence of the target sequence. Mice could respond to the earliest possible cues allowing discrimination, effectively solving the task as a 'detection of change' problem, but performed better when responding later, after more evidence could be collected.

Sequence selectivity can emerge generically in neurons through widespread forms of synaptic plasticity, and our expectation was that learning the task would induce cortical neurons to refine their sensory tuning simply by becoming more selective to the target sequence. Instead, two-photon imaging showed that, upon learning, neurons in both the primary somatosensory cortex (S1) and posterior parietal cortex (PPC) responded to multiple task variables, including not just sensory input but also the animal's action decision (goal-directed licking) and the trial's outcome (presence or absence of the predicted reward). However, optogenetic inactivation showed that while S1 was necessary for sequence discrimination, PPC was not. This indicates a dissociation between the response properties or "codes" that neurons in a cortical area exhibited in the task, and the causal involvement of that area in the task.

Our results show that (1) conditioning on a goal-directed sensory discrimination task results in neurons within sensory and association cortex whose activity reflects the learnt links between target stimulus and licking; (2) cortical neuronal activity reflecting task variables can simply broadcast those variables without playing a causal role in task performance.

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PS3-40

Neural probes for multimodal interrogation of brain lamination

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Understanding the laminar organization of brain areas is crucial to appreciate function and dysfunction. A diversity of cell types and input pathways distribute unevenly through neocortex and brain areas. Regional differences of cell-type specific innervation by local GABAergic interneurons shapes brain parcellations. Importantly, recent studies suggest that in some regions, such as the hippocampus, a more granular lamination can be defined across the CA1 deep and superficial sublayers. Strikingly, this fine-grained microstructure is revealing critical to evaluate histopathological entities associated to a range of neurological diseases.

Here, we describe a toolbox of neural probes suitable for evaluating the laminar organization of the brain at the neurophysiological, optogenetic and spectroscopic levels. Using ultra-dense Neuropixel probes, we obtain laminar recordings and well-isolated spiking activity of hundreds of neurons across several brain regions. Non-canonical 3D-oriented penetrations allow for simultaneous assessment of neocortical, hippocampal and brainstem nuclei of awake head-fixed mice. Using spectral analysis and unsupervised spike sorting techniques, we isolate the different contribution from neocortical and hippocampal activity, which when histologically validated permits resolving neurophysiological laminar profiles at high resolution. Next, we use high-density silicon probes with integrated micro-light emitting diodes (LEDs) combined with cell-type specific optogenetic for dissecting sublayer composition in the hippocampal area CA1. We show successful optotagging of a wealth of different neuronal types, including pyramidal cells and a diversity of GABAergic interneurons. Finally, we map depth-resolved Raman signals using tapered optical fibers to obtain spectroscopic laminar profiles of the chemical composition of brain parenchyma. We identify specific Raman signatures of fatty acid and triglycerides, as well as lipid and proteins differentially expressed across brain depth, which can be tracked histologically.

We discuss how this sophisticated toolbox of neural probes may allow for an unprecedented multimodal evaluation of brain structure and function in health and disease

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PS3-41

Cognitive effects of physical exercise are inherited by the second generation

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Physical exercise has a positive impact on brain and cognition. Previous results from our laboratory confirmed that these positive effects are not only present in animals that went through a forced protocol of exercise of moderated intensity (F0), but also in their sedentary male offspring (F1). Both exercised fathers and their litters had a cognitive advantage in behavioural tests that evaluate recognition memory and pattern separation abilities, and had increased levels of adult hippocampal neurogenesis. These results were replicated in three different experimental designs and the transmission via paternal lineage was confirmed. In the present work we tested if these effects are also inherited by a second generation (F2). Results indicate that the cognitive advantage reaches the F2, but are not accompanied by increased levels of adult hippocampal neurogenesis.

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PS3-42

A scalable and physical approach to the study of spatial navigation and its components

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Spatial navigation is a very complex, multi-process function. In humans it is often studied using computer programs (via virtual reality or through a regular computer screen). Our goal was twofold: first, to create an apparatus to study spatial navigation in a more lifelike, less abstract approach, where subjects navigate through a real space. Second, to use this device to disaggregate and evaluate the components of spatial navigation through different tests.

We built a cylindrical structure (3 meters in diameter and height) with 5 computers connected to 4 led matrixes and a motorized laser. Everything is wirelessly controlled via WiFi. Two protocols were designed to specifically evaluate the different reference frames used during spatial navigation (i.e., egocentric and allocentric). The allocentric evaluation protocol consists of finding a goal's position (signaled by shining a laser on the floor) relative to spatial cues displayed through the led matrixes. The egocentric evaluation protocol is a scalable maze-like test simulating a grid of successive structures. This is accomplished by making the subject to enter and exit the structure through specific places to advance to the "next" position. Different positions are achieved by showing consequent combinations of images and cues on the led matrixes. Both protocols have a computerized version to (i) achieve a more reliable evaluation of the allocentric component, (ii) to compare the strategy and score differences between physical and virtual protocols, and (iii) to make a non-priming longitudinal evaluation.

We are currently validating the difficulty of the protocols for different scenarios, as we are planning to study how several pathologies (Alzheimer's disease, autism spectrum disorders, Parkinson's disease…) and variables (physical exercise, transcranial direct current stimulation, transcranial magnetic stimulation, age…) affect performance and strategies in each test.

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PS3-45

Conditional deletion of the Cntnap2 gene in mice: a phenotypic study

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One of the most accepted theories about the pathogenesis of Autism Spectrum Disorder (ASD) is the alteration in the proportion of excitatory projection neurons (PNs) and inhibitory cortical neurons (cINs). Similar to findings in humans, the mouse model of autism, knockout for the Cntnap2 gene, displays migration abnormalities of PNs and reduced number of cINs and associated alterations in both the excitatory and the inhibitory networks.

Hence, the aim of our work is to decipher how each specific class of neurons contributes to the pathophysiology of ASD. For this, we have generated two conditional mouse models with specific forebrain deletion of Cntnap2 in either cINs or PNs by means of cre-lox technology.

Behavioral characterization of the models involves tests for the core domains of autism, including vocal communication, social behavior, and repetitive behavior, as well as tests for autism-related behaviors such as hyperactivity and sensory reactivity, shown to be altered in the full Cntnap2 KO mouse. Preliminary results in both conditional KO mouse models did not find a significant difference between the conditional mice and their controls in any of the tests.

These results suggest that the absence of Cntnap2 gene exclusively in cINs or in PNs do not seem to be enough to cause the ASD phenotype. Further studies are needed to identify the involvement of other neurons from different networks in the deficits observed in the KO full model.

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PS3-46

Cerebellar Interpositus Nucleus Activities Underlying Classical Eyeblink Conditioning in Rabbits

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It is generally accepted that learning is a functional state of the brain that can only be fully understood during the very moment of its acquisition, storage or retrieval. We believe that learning and memory are distributed functional states (rather than localized, transient processes) requiring the participation of numerous neural structures and their proper and timed activation. The generation of new motor abilities is an essential component of the learning process. In this regard, we studied cerebellar interpositus nucleus (INTn) functioning by recording its unitary activity in behaving rabbits during an associative learning task (classical eyeblink conditioning). The reason is that the INTn has been related to the generation of the conditioned eyeblinks but is still unclear its specific role compared to other brain motor areas. We recorded INTn neurons in chronically implanted rabbits during classical eyeblink conditioning using a delay paradigm. We identified INTn neurons by their antidromic activation from the contralateral red nucleus and synaptic activation from the facial motor cortex. We have compared the activity of INTn neurons during classical eyeblink conditioning with those already collected in the same species from the contralateral somatosensory, motor and prefrontal cortices, as well as the contralateral red nucleus, and the ipsilateral facial motor nucleus. In this way, we will show for the very first time a complete picture of the firing activities of neurons located in the main brain motor areas during the performance of the same associative learning task.

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PS3-47

Characteristics of the spontaneous blinking depending on the attentional conditions and the sensory nerve activity from the ocular surface

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Control of spontaneous blinking lies in a brainstem center that determines blinking pattern, which is influenced by the attentional state. Contrarily, reflex blink is produced in response to the increased activity of the sensory neurons innervating the eye surface and its annexes. We hypothesize that spontaneous blinking is also driven by sensory input. The aim of this work was to establish whether the pattern and characteristics of spontaneous blinking is modified or not by the activation or inhibition of ocular sensory nerves under different attentional conditions.

Orbicularis oculi muscle electrical activity (OOEmg) was recorded in 12 young healthy volunteers (7 women/5 men) using surface electrodes in three conditions (5min each): at rest (basal), and performing visual and non-visual tasks. Spontaneous blinking frequency (BF), inter-blink interval (IBI), and OOEmg amplitude and duration were analyzed in the three conditions. In a different day, OOemg recording protocol was repeated after receiving topically a drop of either perfluorohexyloctane (F6H8; that decrease the ocular surface temperature) or the local anaesthetic tetracaine/oxybuprocaine (1/4 mg/ml).

Compared with basal values, BF was lower during visual tasks and higher during non-visual tasks. During any task OOemg signal amplitude was larger and OOemg duration was shorter than at rest. BF increased significantly and IBIs were more regular after F6H8 treatment, in all three conditions, also increasing the amplitude and decreasing the duration of OOemg signals. Treatment with local anaesthetic did not significantly modify the parameters studied.

Present results confirm that the central blink generator controlling spontaneous blinking is regulated by higher brain centers, which reduce blink frequency and duration during visual attention tasks. Data also suggest that both the frequency and pattern of spontaneous blink is highly influenced by the increase of the sensory input from cold thermoreceptor endings innervating the ocular surface.

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PS3-48

Sensory independent history choice biases in auditory categorization tasks in rats

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To make adequate decisions, animals need to evaluate not only the current sensory information but also recent actions and outcomes. In trial-based perceptual categorization tasks, both humans and rats can develop three main history choice biases: (1) the win-stay/lose-switch bias, which reflects a tendency to repeat previous rewarded actions and avoid unrewarded ones; (2) a repulsive aftereffect caused by previous stimuli and related to sensory adaptation; and (3) the transition bias, a tendency to repeat or alternate the previous response based on an internal estimate of the repeating probability of the sequence of events. While the first is known to be an action-reward bias, the last two are assumed to be sensory-related, but few studies have validated this hypothesis. To do it, we trained rats on two tasks which only differ in the existence of sensory information.

First, to test if the Aftereffect bias is affecting the perception of upcoming stimuli, we trained rats in an auditory categorization task (Sound task) with a 10% of Silent catch trials. With this design, animals could generally use sounds to guide their choices. We found that animals still exhibited an Aftereffect bias in Silent trials, suggesting the bias does not require the perception of a stimulus to impact consequent choices. Second, to elucidate which is the contribution of sensory stimuli to generate the Transition bias, we trained rats in a free-choice task (Foraging task) in which there were no acoustic stimuli to guide their choices, and animals had to rely solely on the serial correlations of the sequence of previous choices to obtain reward. We found that rats developed the same Transition bias as in the Sound task, suggesting that it reflects the prediction of the rewarded response rather than an expectation of future stimuli.

These results suggest that the three more prevalent history biases observed in rats performing a decision-making task -win-stay/lose-switch, transition and aftereffect- can all be manifested in the absence of a sensory stimulus.

PS3-49

Coaching and Human Brain Creativity Mechanisms

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The coaching profession has been in a situation of both methodological and identity uncertainty for a long time, which causes a continuous misunderstanding regarding its practice and essence. The purpose of this study was, in the first place, to demonstrate, from the experimental point of view, how coaching of non-directive essence, with its competencies framework and its essence of non-transference of knowledge or judgment, is capable of enhancing the brain's creativity mechanisms of human beings. Secondly, it was necessary to provide psycophysiological evidence of the effects of non-directive coaching (NDC); and, thirdly, to frame coaching also within a specific field, such as creativity. This also allowed to identify coaching as a profession that helps to cover the current gap regarding the growing decrease of creativity in the human being that has been taking place for two decades; and, on the other hand, it contributed to react in an effective way to the challenges of this uncertain and complex world. For this purpose, an experimental methodology was developed, where the response of the subjects to three conditions (rumiative, directive and non-directive) was compared through electroencephalographic (EEG) measurement during problem solving and achievement of goals. For this, 16 subjects (8 men and 8 women) participated. The study allowed the detection of a series of differentiated and specific EEG patterns in the third condition (non-directive) related to the results found in previous studies on creative insight. Results showed significant changes in alpha and theta frequencies in the right temporal region, and alpha, theta and gamma in the right parietal region, compared to other experimental conditions. Thus, the application of the methodological framework of the NDC was related, in a specific way, to the creativity and the development of human knowledge.
Keywords: non-directive coaching, electroencephalography, insight, creativity.

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PS3-50

MicroRNAs signatures for vulnerability to food addiction.

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Food addiction is characterized by a loss of behavioral control over food intake leading to obesity and eating disorders. We used a mouse model of food addiction to classify extreme subpopulations of vulnerable and resilient phenotypes to identify differential miRNA signatures. Subsequently, we choose three candidate miRNAs down-regulated in addicted mice and performed a functional validation to recapitulate the vulnerable phenotype. The validation was performed by a Tough-Decoy inhibitor delivered by an adeno-associated viral vector through a stereotaxic surgery into the mPFC. Interestingly, we demonstrated that the inhibition of two candidate miRNAs recapitulated the vulnerable phenotype, increasing the persistence or the compulsivity, respectively, underlining the specificity of their effect in the resulting phenotype. The manipulation of the third candidate gene did not have any significant effect in the vulnerability to addiction. In addition, we also characterized other phenotypic traits more subtle but also related to the vulnerability towards addiction. The elucidation of the epigenetic mechanisms underlying these behavioral alterations provides new advances toward innovative and effective interventions for this disorder.

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PS3-51

EXPLORING NETWORK CODING STRATEGIES THAT COULD BE ESSENTIAL FOR THE PROPER EXECUTION OF BEHAVIORAL SEQUENCES DURING AN OPERANT CONDITIONING TASK

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Humans remember events as they occur in a sequential order in time, such as before or after another event. Interestingly, patterns of behavior occur in a temporal sequence that determines the order in which behaviors unfold in time (i.e., a behavioral sequence). Behavioral sequences (also referred to as sequential learning) are arguably the most prevalent form of human and animal learning and they play a pivotal role in conventional studies of operant conditioning. The goal of this experimental-analytical study was to identify the conditions under which the activity-dependent changes in synaptic strength could be directly affected by an operant conditioning task, which is determined by several levels of expression of the conditioned response, different performances of the animal behaviors and also by different execution degrees of their behavioral sequences. To accomplish this goal, we recorded the field evoked potentials and exhaustively analyzed the synaptic-strength changes taking place at 13 selected sites of the cortical (hippocampal, medial prefrontal cortex) and subcortical (thalamus, amygdala, accumbens septi) circuits during the performance of 8 different behaviors related (to a greater or lesser degree) to the acquisition of an operant conditioning by alert behaving rats and also during the execution of specific temporal sequences of rat behaviors directly related to this type of associative learning task. Collected results allow to verify a large spatio-temporal diversity of synaptic-strength changes during the performance of different rat behaviors (locomotor, appetitive, consumatory, exploratory or stationary). In addition, the findings reported here seem to support a more selective repertory of underlaying rules based on modular integrations of the synaptic-strength changes and on spatio-functional propagation patterns of the evoked field potentials — i.e., two network coding strategies that could be essential for the proper execution of specific temporal sequences of animal behaviors during operant conditioning tasks.

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PS3-52

The steroid sulfatase inhibitor STX64 improves age-associated cognitive deficiencies

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Aging produces in brain a progressive oxidative process and neuroinflammation that deteriorates cognition. These brain dysfunctions provoke high economic and social cost to developed societies. For this reason, the search for treatments to prevent cognitive deficits associated with aging is a priority. Previous results suggest that STX64, a steroid sulfatase (STS) inhibitor, improves cognition in neurodegenerative diseases. Here we have designed cellular (immunohistochemistry), molecular (qPCR) and behaviour (mainly, object recognition and passive avoidance for the study of learning and memory) assays to know if subchronic oral treatment with STX64 can rescue cognitive dysfunction present in aging mice. Our behavioural results show that STX64 treatment improved cognition in aging mice, reflected as an improvement in object recognition and in passive avoidance tests. At cellular level, aging mice treated with STX64 showed an increase in microglial response and an increase in hippocampal adult neurogenesis. By last, preliminary qPCR assays indicated that hippocampus from aging mice treated with STX64 express lower levels of inflammatory factors mRNA compared with untreated aging mice. Then, our results indicate that STX64 may be a drug with potential therapeutic interest for the treatment of cognitive deficits associated to aging.

PS3-53

One-shot learning in recurrent networks using behavioral time-scale plasticity

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The formation of episodic memory requires fast and potent plasticity mechanisms which allow for one-shot association of events on a time-scale of seconds or longer. Traditional Hebbian plasticity rules rely on the concurrence of pre- and post-synaptic spiking and typically lead to plasticity windows of only tens to hundreds of milliseconds. Furthermore, such rules tend to lead to instabilities unless the learning occurs slowly, making them inappropriate for one-shot learning.
However, recent in-vivo experiments in area CA1 of mouse hippocampus have revealed a new form of plasticity, dubbed Behavioral Time-scale Plasticity (BTSP), which leads to the rapid formation of place fields in previously silent cells, or the shifting of place field location in place cells. BTSP relies on the coincidence of pre-synaptic firing and a global, dendritic-wide post-synaptic signal consisting of a broad Ca2+ spike, which results in a plasticity window of several seconds or more. These plasticity effects are quantitatively fit by a computational model in which the amplitude and direction of plasticity of a given synapse depend on presynaptic firing, the current state of the synapse, and a global signal. However, this model is dynamically complex and is not amenable to analysis, making it difficult to investigate the role of such a plasticity rule in memory formation in large recurrent networks.
Here we propose a simple one-dimensional map for synaptic plasticity which qualitatively captures all relevant features of BTSP. Specifically, we can reproduce rapid place-field formation and shifting as well as the dependence of place-field width on the velocity of motion of the animal. Our map can furthermore be straightforwardly extended to recurrent networks, allowing for the analytic derivation of memory capacity for one-shot learning. We find that the weight-dependence of the rule leads to the classical stability-plasticity trade-off in learning by which older memories decay through overwriting.

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PS3-54

META-ANALYSIS ON NEURAL DATA: A COMPARISON BETWEEN DIFFERENT APPROACHES TO SPIKE-SORTING ON CLAUSTRUM MULTI-UNITARY ACTIVITY

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Recent advances in signal acquisition systems which allow neuronal recordings up to hundreds of channels simultaneously results into substantial time consuming and basic signal processes limitations. Within spike-sorting, the accuracy of the overall analysis is dependent on every step of the procedure. Spike clustering alongside feature extraction are critical steps after an appropriate data preprocessing. Some methods developed during the past few years have been focused on reducing the amount of computation required for spike-sorting by a mathematical simplification of the raw data. Often, these algorithms trend over use mathematical entities to predict waveforms rather than use physiological features, which results in the loss of interpretability due to a misapplication of extracted features. As far as we know, meta-analysis (i.e., examine and combine results from several analytical-experimental approaches) applied to neuronal spike-sorting are uncommon. In this work, we chose Kilosort, the latest and most influential algorithm for spike-sorting, as the perfect counterpart to VISSOR, an approach based on shape, phase, and distribution features of each spike, which reveals functional information of the neural events under study. Kilosort needs from voltage measures at closely-space sites which enable the algorithm to use together spatial and temporal shape features. The key aim is to compare the two aforementioned approaches applied to Claustrum (CL) multi-unitary activity during classical eyeblink conditioning: a tone as conditioned stimulus (CS) and an air-puff as unconditioned stimulus (US). Neurons were recorded using 16 channels proves with the aim of reaching the whole length of the CL. According to our results, Kilosort is functional for high-density recordings due to its novel spike-sorting framework, but its performance was not as enlightening as expected, when the inter-stimulus interval (CS-US), in which the neural correlates should be determined, is very short (250 milliseconds) and the number of electrodes is limited (e.g., 16 channels).

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PS3-55

Specialized prefrontal circuits explain population dynamics during working memory encoding and maintenance

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Neuronal population activity recorded from primate prefrontal cortex (PFC) carries information about the presented stimulus during working memory tasks. During cue presentation and in the beginning of the delay period the population code is dynamic [1], before it stabilizes and remains stable throughout the rest of the delay period. The circuit mechanisms underlying this dynamic-to-stable transition in the code are not yet understood. Here, we show that a spiking network model composed of three specialized attractor circuits can explain these experimental observations. Each conceptual ring circuit represents a specialized PFC sub-population (encoding, storage and readout neurons). Based on experimental data [2] we structured the model such that the stimulus input excites the encoding population while it suppresses the storage population. Since the recurrent connections in the encoding ring are not strong enough, the activity fades upon stimulus removal. However, at the same time the strongly connected storage units are released from stimulus suppression and form the stable bump which will maintain the memory. The readout circuit receives input from the other two populations and is thus active during cue and delay periods even without strong recurrency. Cross-temporal decoding analysis in the model fails to generalize across cue and delay periods because different neuronal subsets are most informative during the respective epochs. We validated the specific decoding pattern in PFC recordings from a visual and memory task [2] Finally, from a functional point of view, the network model predicts increased robustness to distractors once the activity bump has formed in the storage population. In sum, our findings suggest that the presence of a highly dynamic cue to delay transition originates mainly from different neuronal subpopulations. After this initial transient, a stable state is reached, and memory maintenance is achieved through attractor dynamics.

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PS3-56

Synaptic extension of the bump attractor model predicts target-distractor onset asynchrony effects

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Distractor filtering is fundamental to achieve an efficient management of working memory (WM). The capacity of a distractor to impair WM performance depends on its time separation with the target stimulus, the target-distractor onset asynchrony (TDOA). Distractors are more disruptive for short than long TDOA. This fact suggests a period of relative memory instability at early stages of the WM delay period, but its exact mechanisms remain elusive. The bump attractor model of WM explains memory maintenance through elevated firing activity during the delay period, and it can explain the TDOA effect by assuming a slow, gradual formation of the attractor in the delay. Here, we propose an alternative model based on the interplay of persistent activity and short-term synaptic plasticity. The combination of synaptic depression and facilitation at the onset of sustained activity induces a transient dip in the firing rate of memory-selective neurons in the early delay period. We tested this specific prediction by reanalyzing single-neuron recordings in macaque dorsolateral prefrontal cortex (dlPFC) and lateral intraparietal area (LIP) while performing a visuo-spatial WM task with distractors presented with TDOAs of 100, 200, 300 and 900ms [1]. Consistent with the model, we found that neurons selected based on their target stimulus selectivity at the end of the delay displayed a short drop in firing rate following elevated firing in the cue period. We also tested the validity of the model in human participants performing a more complex task where, besides manipulating the TDOA, distractors were presented not just after but also before the target. Behavioural, modeling and electrophysiological results point towards a dlPFC population that combines circuit-reverberation and short-term synaptic plasticity mechanisms to achieve distractor-resistant memory maintenance.

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PS3-57

STUDY OF BONE MARROW-DERIVED MICROGLIAL CELLS IN A MODEL OF SELECTIVE NEURODEGENERATION

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The Purkinje Cell Degeneration (PCD) mouse presents a mutation in the Ccp1 gene that produces the selective post-natal death of Purkinje cells. Along with this neuronal loss, a strong microgliosis takes place in the cerebellum, but it is not fully understood whether it plays a beneficial or a harmful role in the development of the pathology. In this sense, it is also unknown if this gliosis is a direct consequence of the neurodegeneration, or if, by contrast, the pcd mutation itself causes an aberrant microglial behavior. Therefore, the direct effect of the pcd mutation on the functioning of the microglia was studied using cell cultures, without the influence of a neurodegenerative environment.

For this purpose, hematopoietic cells were isolated from the bone marrow of both wild-type and PCD mice and differentiated into microglia. Subsequently, immunofluorescence techniques and qPCR analyses were performed to characterize microglia by studying different markers and gene expression. Likewise, the viability of these cells was studied by means of a proliferation essay with Alamar Blue.

The preliminary results obtained suggest that the hematopoietic cells of PCD mice differentiated into microglia have a predominant polarization towards an anti-inflammatory phenotype. Besides, a differential gene expression has been observed for all the analyzed genes. Finally, the Alamar Blue essay demonstrated that PCD cells show a higher proliferation than the wild-type cells.

Therefore, it can be concluded that the mutation of the Ccp1 gene affects some microglial features related to cell morphology and neurochemical, gene expression and proliferation.

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PS3-58

The loss of starburst amacrine cells and their synaptic contacts with dopaminergic amacrine cells may explain the visual motion perception disturbance in Parkinson's disease.

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The main clinical characteristic symptoms of Parkinson's diseases (PD) are bradykinesia, tremor, and other motor deficits. However, there are other non-motor symptoms that can be identified at early stages of the disease, such as visual disturbances. One of these symptoms is the impairment of the motion perception. Therefore, the purpose of this study was to determine if the starburst amacrine cells (direction-selective amacrine cells), which is the main cellular type involved in motion perception, are degenerated in PD and if the dopaminergic system is related to this degeneration.

Human eyes from control and PD donors were available for this study. Dopaminergic amacrine cell density (tyrosine hydroxylase positive cells), starburst amacrine cell density (choline acetyltransferase positive cells), and their synaptic contacts (vesicular monoamine transporter-2 positive presynapses) were evaluated by immunohistochemistry and confocal microscopy in whole-mount retinas.

We observe that the number of dopaminergic amacrine cells was significantly decreased in PD retinas. Also, there is a degeneration of starburst amacrine cells observed by a decrease in the density of these cells in the two plexuses where they are located. Importantly, here we describe for the first time that dopaminergic amacrine cells contact with choline acetyltransferase positive cells in healthy control retinas and that these connections decrease in PD.

This work indicates that dopamine could modulate starburst amacrine cells and that the decrease of this input in PD may explain the degeneration of starburst amacrine cells that we describe and thus, the motion perception disturbance in this pathology.

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PS3-59

CONTRIBUTION OF THE PRIMARY SOMATOSENSORY CORTEX TO REFLEX BLINK IN NAÏVE AND TEAR-DEFICIENT RATS

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Reflex blinking (RB) evoked by natural stimulation of the ocular surface (OS) is integrated in the brainstem. There is scarce evidence of its modulation by higher structures. The aim of the present work was to analyse the contribution to RB of the area of the primary somatosensory cortex (S1) where OS is represented, both in naïve and tear-deficient rats.

Multiunit activity of S1 neurons and electromyographic activity of the contralateral orbicularis oculi muscle (OO-EMG) were simultaneously recorded using high-impedance tungsten and silver electrodes, respectively, in 17 male Wistar anesthetized rats (8 naïve; 9 tear-deficient, previously subjected to lacrimal gland excision). RB was evoked by electrical stimulation of the OS at 0.1 Hz and different intensities, before and during application of 2% lidocaine to S1, and after drug washout. S1 activity was reduced or fully abolished by lidocaine.

In naïve animals, evoked OO-EMG activity preceded S1 activation. The area under the curve (AUC) of the evoked OO-EMG signals increased significantly during S1 anesthesia (0.007±0.009 vs. 0.013±0.013 V2, n=16 eyes, $p<0.01$). In tear-deficient rats, similar AUC values were obtained before (0.023±0.003 V2, n=18 eyes) and during S1 anesthesia (0.022±0.002 V2), although AUC was significantly larger than in naïve animals, both before ($p<0.001$) and during lidocaine application ($p<0.01$).

Results show that the activity of the somatosensory cortex modulates reflex blink characteristics in health conditions. In chronic tear deficiency there is an increased sensory input that drives orbicularis oculi activity, which appears not to be regulated by cortical activity.

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PS3-60

MATERNAL SEPARATION DECREASES THE EXPRESSION OF DOUBLECORTIN IN THE OLFACTORY SYSTEM OF BOTH MEPC2-HETEROZYGOUS FEMALE MICE AND THEIR HEALTHY CONTROLS

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Mutations in the X-linked gene MECP2 are the main cause of Rett syndrome, a rare disease affecting females, and other neurodevelopmental disorders. This gene codes for methyl CpG binding protein 2, a transcriptional regulator expressed in neurons. Our previous data show that the density of immature neurons, expressing doublecortin, is significantly higher in the piriform cortex, but not in the olfactory bulbs or the hippocampus, of symptomatic Mecp2-mutant mice, as compared to their age-matched wild-type controls. Since previous pieces of evidence suggest an effect of early life stress in neuronal maturation, here we sought to analyze the impact of maternal separation, and its interaction with Mecp2 deficiency, in the expression of doublecortin in the postnatal brain. To do so, we performed a double immunofluorescent detection of doublecortin and NeuN, a marker of mature neurons, in adolescent Mecp2-heterozygous and wild type female mice that were either subjected to 3 hours of maternal separation from postnatal day 3 until weaning, or left undisturbed with the dam. The effects of genotype and type maternal care were analyzed using the classical frequentist ANOVA and Bayesian inference. Both statistical analyses revealed a significant increase in doublecortin expression in the olfactory tubercle in Mecp2-heterozygous females irrespective of maternal care. By contrast, doublecortin expression was decreased in the piriform cortex and granular cell layer of the olfactory bulbs of females subjected to maternal separation, irrespective of their genotype. Similarly, the percentage of doublecortin/NeuN cells in the periglomerular layer of the olfactory bulbs was decreased in both groups of maternally-deprived females. Finally, we found no effect of either genotype or maternal deprivation in doublecortin expression in the dentate gyrus of the hippocampus. Our results suggest that early environmental intervention could help rescuing region-specific deficits in neuronal maturation in Mecp2-mutant mice. Funded by Ministerio de Ciencia e Innovación (PID2019-107322GB-C22).

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PS3-61

Acute cocaine enhances dopamine D2R recognition and signalling and counteracts D2R internalization in Sigma1R-D2R heteroreceptor complexes

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The current study was performed to establish the actions of nanomolar concentrations of cocaine, not blocking the dopamine transporter, on dopamine D2 receptor (D2R)-sigma 1 receptor (δ1R) heteroreceptor complexes and the D2R protomer recognition, signaling and internalization in cellular models. We report the existence of D2R-δ1R heteroreceptor complexes in subcortical limbic areas as well as the dorsal striatum, with different distribution patterns using the in situ Proximity Ligation Assay. Also through BRET these heteromers were demonstrated in HEK293 cells. Furthermore, saturation binding assay demonstrated that in membrane preparations of HEK293 cells coexpressing D2R and δ1R, cocaine (1nM) significantly increased the D2R Bmax values over cells singly expressing D2R. CREB reporter luc-gene assay indicated that coexpressed δ1R significantly reduced the potency of the D2R like agonist quinpirole to inhibit via D2R activation the forskolin induced increase of the CREB signal. In contrast, the addition of 100nM cocaine was found to markedly increase the quinpirole potency to inhibit the forskolin induced increase of the CREB signal in the D2R-δ1R cells. These events were associated with a marked reduction of cocaine induced internalization of D2R protomers in D2R-δ1R heteromer containing cells vs D2R singly expressing cells as studied by means of confocal analysis of D2R-δ1R trafficking and internalization. Overall, the formation of D2R-δ1R heteromers enhanced the ability of cocaine to increase the D2R protomer function associated with a marked reduction of its internalization. The existence of D2R-δ1R heteromers opens up a new understanding of the acute actions of cocaine.

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Dysregulation of the autophagic-lysosomal pathway in Parkinson's disease associated to GBA

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Parkinson's disease (PD) is characterized by the death of dopaminergic neurons from the substantia nigra pars compacta and the presence in the affected brain regions of intracytoplasmic protein inclusions called Lewy bodies (LB). The main component of LB is α-synuclein, a protein prone to form neurotoxic oligomers and aggregates in a concentration-dependent process. Since increased levels of α-synuclein can promote PD progress, the turnover mechanisms of this protein play an important role in PD development. Particularly, the autophagic-lysosomal pathways have a key role in maintaining proper α-synuclein neuronal levels.

The first genetic risk factor to develop PD is the presence of mutations in the GBA gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase) involved in sphingolipids metabolism. About 12% of PD patients present a mutation in GBA and more than 50% have pathogenic mutations in lysosomal enzymes, emphasizing the key role of the lysosomal function in PD. An inverse relationship between loss of GCase activity and α-synuclein accumulation has been shown in different PD models and in samples from PD patients carrying GBA mutations. This increase in the intracellular levels of α-synuclein is one of the main causes that contribute to neurodegeneration in PD.

We have characterized the role of the autophagic-lysosomal function and the presence of α-synuclein neurotoxic species in a new in vitro model of differentiated dopaminergic-like neurons expressing the two most prevalent GBA mutations, p.N370S and p.L444P, as well as GBA knock out. We observed that loss of GCase activity leads to the cellular and intralysosomal accumulation of GCase substrates, lysosomal dysfunction, macroautophagy and CMA impairment, mitochondrial dysfunction, ROS production, ER stress and ultimately increase of different α-synuclein species.

We are using this cellular model as a valuable in vitro system for the screening of a therapeutic approach based in the restoration of GCase activity in lysosomes through enzyme replacement therapy enhanced with nanotechnology. Restoration of the autophagic-lysosomal system may promote α-synuclein turnover and avoid the accumulation of α-synuclein PD-associated neurotoxic species.

PS3-63

P53 DEPLETION PROMOTES NEOVASCULARIZATION AND BRAIN REPAIR AFTER INTRACEREBRAL HEMORRHAGE

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Brain neovascularization has been associated with good prognosis of intracerebral hemorrhage (ICH) patients. We previously showed that the human Tp53 Arg72Pro SNP modulates brain endothelial cells survival after ICH, which is essential for the secretion of growth factors and cytokines (i.e. VEGF) that mediate the mobilization of endothelial progenitor cells (EPCs) from the bone marrow to the peripheral blood. EPCs promote brain vascular repair after ICH. Then, pro-apoptotic p53 would be a negative regulator of EPC mobilization, thus affecting the functional outcome after ICH. Since p53 is accumulated in the brain after ICH, we speculate that p53 destabilization not only will promote cell survival, but also vascular recovery and brain repair.

p53 KO mice were subjected to an experimental model of ICH in vivo by injecting bacterial collagenase into the basal ganglia. Proliferative markers (BrdU, Ki67) and perfusion status of newly-formed blood vessels in the brain was also analyzed after Evans blue injection.

We observed that p53 loss reduced lesion volume and significantly boost levels of circulating EPCs in mice from 72 hours after ICH. Knockdown of p53 also increased proliferative events in SVZ and lesion areas, as evidenced by BrdU incorporation and Ki67 staining. Consequently, an improved vascular repair response was achieved in p53 KO mice, in comparison with those expressing an active p53 protein.

Our results point out the impact of the p53 signaling pathway in the balance between brain damage and repair, which might condition functional recovery after ICH.

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Morphometric Cluster Analyses of Sibling NG2-Cells in Response to Multiple Sclerosis Lesion Models

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NG2-cells, also known as oligodendrocyte precursor cells (OPC), are a heterogeneous glial cell population. This heterogeneity is still under debate and whether it can be driven by intrinsic factors, such as their ontogenic origin, remains unclear. Nevertheless, the NG2-glia display different functions during the development and after brain damage. At this respect, we recently revealed the heterogenic response of NG2-glia clones to experimental autoimmune encephalomyelitis (EAE) brain damage. Now, we sought to analyze the relationship between both their morphology and ontogeny in the adult brain and their changes in two different Multiple Sclerosis (MS) models' scenarios. To address this question, we combined the StarTrack, a multicolor genetic lineage-tracing tool that enables the long-term in vivo tracing of progenitor lineages, along with a single-cell morphometric cluster analysis, in the two MS murine models induced by EAE and Cuprizone, to compare with control brains. We correlated the reactivity, with different morphometric parameters measured in the derived NG2-cell progeny of StarTrack targeted single progenitors. Data from the morphometric analysis allowed us to unravel different NG2-cell clusters sorted by morphological parameters related, not just by their ontogenic origin, but also related to the different MS lesions. In summary, a better understanding of NG2-glia heterogeneity is relevant to decipher the physiological role of these cells both in healthy brain and in response to MS.

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PS3-65

Impact of white adipose tissue in AD pathology

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-Alzheimer's disease (AD) is a complex disorder and multiple cellular and molecular mechanisms are involved in AD onset and progression. Recent evidences has suggested that metabolic alterations are an important pathological feature in disease progression in AD. Likewise, diabetes and obesity, two mayor metabolic illnesses, are risk factors for AD. In addition, novel studies has suggested that AD induces peripheral metabolic alterations, facilitating the development of diabetes. Overall, these studies suggest that there is an important two-way crosstalk between AD and peripheral metabolic disorders. Here, we seek to understand the mechanisms underlying this association and we hypothesize that the white adipose tissue may serve as a key communicator organ between the brain and peripheral metabolic illnesses, and alterations in this organ may affect both types of disorders.
-Here, we used histological stains, immunohistochemistry and biochemical means to determine changes in the white adipose tissue from WT and 3xTg-AD mice. Moreover, similar techniques were used in the brain of 3xTg-AD mice that received white fat pads from WT and 3xTg-AD donors to determine any changes in amyloid and tau pathology.
-Our study shows that 3xTg-AD mice develop significant peripheral metabolic alterations which in turn affected the white adipose tissue biology. Moreover, adipose tissue transplanted from donor 3xTg-AD and WT mice into recipient 3xTg-AD mice indicate that AD associated white fat tissue induced profound AD pathology changes in recipient 3xTg-AD mice.
-Overall, our study demonstrate a novel important crosstalk between AD and peripheral metabolic disorders thought white adipose cells. A more profound understanding in these processes may turn in novel and promising therapeutic strategies for AD and metabolic illnesses.

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The role of the striatopallidal indirect pathway in the generation of L-DOPA induced dyskinesias

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Parkinson's disease (PD) is mainly characterized by dopamine depletion in the striatum due to a loss of dopaminergic neurons in the Substantia Nigra pars compacta. Nowadays, the most efficacious treatment for PD is the dopamine precursor 3,4-dihydroxyphenyl-L-alanine (L-DOPA). Nevertheless, abnormal orofacial, limb and trunk involuntary movements known as L-DOPA-induced dyskinesias (LIDs) remain a major complication. Striatal outputs are composed of medium spiny neurons (MSNs), which inhibit the downstream nuclei of the basal ganglia via the direct and indirect pathways. Direct MSNs innervate the Substantia nigra pars reticulata and the internal segment of the Globus pallidus, while indirect MSNs project to the external segment of the Globus pallidus (GPe). Whereas the role of direct MSNs when mediating LIDs has been established, the contribution of indirect MSNs is still elusive. Anyhow, it is known that during dyskinesias, indirect MSNs display a decreased activity.

Our main objective is to determine the role of indirect MSNs in the LIDs of a mouse model of PD. Our hypothesis is that the activation of indirect MSNs will reduce LIDs. To that end, D2-cre recombinase expressing adult mice are lesioned with 6-hydroxydopamine (6-OHDA) in the medial forebrain bundle, promoting Parkinsonian symptoms. Channelrhodopsin expression is selectively induced in indirect MSNs by injection of adeno-associated cre dependent virus in the dorsolateral striatum. Being that direct and indirect MSNs are connected to each other at striatal level, in order to avoid unspecific effects, the optic fibers are implanted on the GPe. Dyskinetic symptoms are induced by repetitive administration of L-DOPA. Our results show the behavioural effect of the optical stimulation of indirect MSNs' terminals in the GPe, performed before and after three daily injections of L-DOPA, at subthreshold and suprathreshold dyskinetic doses. We also examine the combined effect of light stimulation and an acute L-DOPA treatment.

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PS3-67

Dopamine D4R restores morphine-induced impairment of adult neurogenesis in the subventricular zone

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In the adult mammalian brain, neuroblasts from the subventricular zone (SVZ) migrate along the rostral migratory stream into the olfactory bulb, where they differentiate and synaptically integrate to contribute with the maintenance of the olfactory function. It has been established that endogenous as well as exogenous opioid signalling affects proliferation in adult brains. In fact, chronic administration of morphine reduces adult neurogenesis in SVZ although its implication in addiction has not yet been clarified. On other hand, dopamine has been also identified as a regulatory factor of adult neurogenesis as dopaminergic cells from the substantia nigra compacta project toward the dorsal SVZ whereas the ventral tegmental area innervates the ventral SVZ. Previous results demonstrated that morphine increases striatal dopamine signaling, which is restored by the specific stimulation of dopamine D4 receptor (D4R). The mechanisms by which D4R counteracts morphine effects is not completely understood, but the existence of a D4R-MOR heterodimer in the striosomes of the caudate putamen has been proposed . However, it is unknown how this interaction could affect both the adult neurogenesis and olfaction.

In the present work, we have studied the effects of a chronic treatment with morphine alone or in combination with a D4R agonist (PD168,077) on adult neurogenesis occurring in the SVZ. Furthermore, the impairment or improvement of odorants discrimination has also been analyzed.

Using immunohistochemical techniques, we found that chronic treatment with morphine increases dopamine signalling in the SVZ and promotes a depletion of cell proliferation, affecting both neural and glial precursors. These effects were counteracted by the coadministration of morphine with the D4R agonist. The present results support for a critical role of the D4R to prevent morphine effects in the SVZ.

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PS3-68

Role of dopamine D4 receptor in the development of morphine-induced analgesic tolerance

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Morphine is one of the most effective analgesic used in the clinical management of pain. However, long-term use of morphine can cause many side effects including respiratory depression, constipation, analgesic tolerance, hyperalgesia and addiction. The mechanisms underlying morphine tolerance are complex and nowadays it is not yet completely understood. As a primary mediator of morphine analgesia, the mu opioid receptor (MOR) contributes to morphine tolerance through downregulating the expression of MOR and its uncoupling from G-proteins in the dorsal horn of the spinal cord. It has been reported that the colocalization of the dopamine D4 receptor with MOR in the dorsal striatum counteracts the addictive effects induced by morphine through a putative D4R-MOR heteroreceptor that modulates dopamine signaling from nigral dopamine nerve cells. As D4R is also expressed in both the dorsal root ganglia (DRG) and dorsal horn neurons, we hypothesize that D4R could interfere the development of morphine-induced tolerance to its analgesic effects at dorsal horn level.

Using a chronic treatment paradigm of morphine with the D4R agonist PD168,077, we have first investigated the nociceptive response to noxious thermal stimulation (tail flick), mechanical stimulation (von Frey) and to persistent noxious chemical stimulation (formalin). Furthermore, using immunohistochemical techniques, we have studied primary afferent fibers (peptidergic and non-peptidergic C fibers), spinal interneurons and NK1 spinal projection neurons, and the balance between glutamate and GABA in the dorsal horn.

Results from the evaluation of analgesic activity showed that D4R activation prevents the development of morphine-induced analgesic tolerance. In addition, D4R preserves the appropriate balance between glutamate and GABA for a proper analgesic effect by modulating the spinal circuit. The present results give support for the existence of antagonistic functional D4R-MOR receptor-receptor interaction in the dorsal horn that could help to the development of a new pharmacology strategy in the treatment of pain.

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PS3-69

Oligodendrocyte maturation and myelination: Implications of deficient thyroid hormone transport to the brain.

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Oligodendrocytes are glial cells that play a crucial role in the CNS. Their maturation and myelination are finely regulated processes that require key trophic signals important for growth and metabolism. Thyroid hormone (TH) is a potent signal that regulates oligodendrocyte maturation, oligodendroglial-synaptic interactions and myelination. TH transport across the blood-brain barrier and cellular membranes is mediated by a specific transmembrane transporter, the monocarboxylate transporter 8 (MCT8). Dysfunction of MCT8 leads to inherited hypomyelination and psychomotor disabilities in the X-linked Allan-Herndon-Dudley syndrome (AHDS) or MCT8-deficiency. Although impairments in myelination in AHDS patients represent one of the main hallmarks of the disease, there is no consensus on whether there is a permanent hypomyelination or a delay on myelination that is restored later in life.

To address this point, we made use of multiple techniques to study myelination processes in Mct8/Dio2 knockout mice (KO), an already validated model for AHDS, from postnatal to adult stages, to gain new insight into the pathophysiological mechanisms of AHDS and the effects of TH on myelination.

Myelination was studied histologically by assessing the content of myelin proteins and lipids. These studies revealed persistent myelination defects in the brain of Mct8/Dio2 KO mice, consistent with observations at the ultrastructural level showing severely decreased percentage of myelinated axons in the Mct8/Dio2 KO mice brain using transmission electron microscopy analyses. Myelination was also assessed by Magnetic Resonance Imaging, showing microstructural alterations in the white matter. These data obtained on myelination led to the study on oligodendroglial dynamics, showing altered proliferation and differentiation patterns from oligodendrocyte precursor cell stages.

Myelination and oligodendroglial dynamics in Mct8/Dio2 KO mice are altered from early developmental stages and these alterations persist throughout later stages. Altogether, these data provide new understanding on the pathophysiological mechanisms underlying MCT8 deficiency to design and evaluate possible future treatments.

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PS3-70

Faim knockout leads to gliosis and late-onset neurodegeneration of photoreceptors in the mouse retina

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Fas Apoptotic Inhibitory Molecule protein (FAIM) is a death-receptor antagonist and an apoptosis regulator. It encodes two isoforms that have significant neuronal functions, FAIM-S (short) and FAIM-L (long). FAIM-S, which is ubiquitously expressed, is involved in neurite outgrowth. In contrast, FAIM-L is only expressed in neurons and it protects them from cell death. Interestingly, FAIM-L is downregulated in Alzheimer's disease patients and mouse models before the onset of neurodegeneration, and Faim transcript levels are decreased in retinal degeneration mouse models. Nonetheless, few studies have been directed to elucidate the role of FAIM in the central nervous system, yet alone the retina. The retina is a highly specialized tissue that has proved to precede pathological mechanisms of neurodegenerative diseases. Here we describe that Faim depletion in mice damages the retina unrelentingly and leads to late-onset photoreceptor cell death in older mice. Immunohistochemical analyses show that Faim knockout (Faim-/- mice present ubiquitinated aggregates throughout the retina from early ages. Moreover, retinal cells release stress signals that can signal to Müller cells, as shown by immunofluorescence and qRT-PCR. Müller cells monitor retinal homeostasis, and hereafter trigger a gliotic response in Faim-/- mice that becomes pathogenic when is sustained over time. In this regard, we found a pronounced vascular leakage at the latter ages, which can be caused by persistent inflammation. These results suggest that FAIM is an important player in the maintenance of retinal homeostasis and support the premise that FAIM could be a plausible early marker for late photoreceptor and neuronal degeneration.

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PS3-71

Effect of macrophages on neurosphere formation and neuronal differentiation of neural stem cells

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Among different damages that affect the CNS, traumatic brain injury, spinal cord injury disease and stroke are major worldwide causes of neurological impairment. These conditions exhibit common characteristics, including temporal break-down of the blood-brain barrier, which leads to the extravasation of molecules and blood cells, and the establishment of an inflammatory environment. The major three cell players to rise inflammation are microglia, astrocytes and infiltrated macrophages, which have shown polarization to the pro-inflammatory (type 1) or anti-inflammatory (type 2) phenotypes. Since inflammation can hinder or support neuronal regeneration, in this work we asked whether inflammatory environments mediated by monocyte-derived macrophages might have an influence on neurogenesis. We studied neurosphere formation and neuronal differentiation of NSCs cultured alone or in the presence of macrophages. Macrophages were derived from adult mouse bone marrow and expanded during seven days prior to the experiments. Thereafter, they were polarized to more cytotoxic (IFN-γ, 8 ng/mL, 24 h) or pro-survival (IL-4, 2 ng/mL, 24 h) phenotypes, or remained inactivated. NSCs were obtained from E11 mouse mesencephalon or adult SVZ, and cultured alone or onto a macrophage monolayer, in the presence of EGF and bFGF, to form neurospheres. To induce neuronal differentiation, growth factors were removed. We observed significantly less neurospheres formation in cocultures with macrophages, compared to controls, however, the proportion of neurons generated, by each neurosphere, was about 8x higher in the case of cocultures. Moreover, mesencephalon-derived neurons exhibited a higher proportion of cells immunoreactive for dopaminergic hallmarks (i.e. TH) and increased neurite outgrowth in the presence of macrophages. We did not find significant differences in neurosphere numbers or neuron ratio between conditions containing inactivated macrophages or pre-polarized to cytotoxic or pro-survival phenotypes. Our results suggest that macrophages modulate the neurogenic and differentiation potential of embryonic and adult NSCs. DMAV is supported by CONACYT(#770727).

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PS3-72

Bile acids reduce glycolysis in proinflammatory macrophages

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Glycolysis is the metabolic pathway that converts glucose into pyruvic acid. CNS pathologies, such as spinal cord injury (SCI) and ischemia, increase the glycolytic pathway in the damaged areas as part of the inflammatory response.
Pyruvate kinase is a key glycolytic enzyme that converts phosphoenolpyruvate and ADP to pyruvate and ATP. In glial cells, pyruvate kinase has two isoforms, PKM1 and PKM2, originated from the same gene. PKM2 has less pyruvate kinase activity than PKM1, but as a monomer or homodimer PKM2 acts as a transcription factor that regulates the expression of target genes involved in glycolysis (e.g. Glut1, LDHA) and inflammation (e.g. IL-1β).
After an injury, both resident (microglia) and hematogenous macrophages are key inducers of the inflammatory response with deleterious effects. We have previously shown that the bile acid tauroursodeoxycholic acid (TUDCA) has anti-inflammatory effects in microglia cells involving the inhibition of NF-κB pathway.
In the present study we have investigated whether bile acids affect the expression of glycolytic enzymes and their regulation by PKM2 in rat microglia cultures and after rat SCI.
Lipopolysaccharide induced the expression of PKM1, PKM2 and its target genes in cell cultures. SCI caused an increase of PKM2 IR in macrophages after SCI. Pretreatment with TUDCA or taurolithocholic acid (TLCA) reduced the expression of PKM2 and its target genes in cell cultures. Similarly, TUDCA treatment reduced the expression of PKM2 in the injured spinal cord.
These results confirm the importance of PKM2 in the inflammatory response in CNS pathologies and indicate a new mechanism of bile acids as regulators of glycolysis.

PS3-73

The effect of bone marrow derived- mesenchymal stem cells on a novel in vitro model of X-linked adrenoleukodystrophy

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X-linked adrenoleukodystrophy (X-ALD) is an inborn error of metabolism caused by a mutation in ABCD1 gene, which encodes a peroxisomal transmembrane protein called ALDP. This protein is involved in the transportation of very-long chain fatty acid (VLCFA) to the peroxisome for degradation. X-ALD patients present an accumulation of VLCFA in tissue and blood due to alterations in ALDP function. The outcome observed in patients with cerebral form of X-ALD is an acute inflammatory demyelination.

The use of bone marrow derived- mesenchymal stem cells (BMSCs) has been studied for many years. BMSCs have been proposed as a therapeutical approach in many diseases.This study will address if BMSCs has a beneficious effect in X-ALD.

Here, we are investigating a novel in vitro model to study X-ALD from dental pulp stem cells (DPSCs), an accessible source of mesenchymal stem cells. DPSCs from a X-ALD patient showed an alteration in ALDP expression and lipid accumulation located in the cytoplasm .

To identify the effect of BMSCs in this in vitro model, we differentiated DPSCs from healthy and X-ALD individuals into neural-like cells. Immunocytochemistry experiments showed the expression of neuronal markers in the differentiated cells.

Electrophysiological assays were carried out to further characterized the neural-like cells. Analysis of the sodium and potassium currents from neural-like cells showed a lower peak amplitude and slower kinetics in X-ALD-derived cells compared to healthy cells.Interestingly, when X-ALD neural-like cells were directly co-cultured with BMSCs, the sodium currents had a larger peak amplitude and faster kinetics, rescuing a healthy phenotype.

Further investigation of the effect of BMSCs on X-ALD cells may provide relevant insights to develop a possible therapy for X-ALD.

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PS3-74

GABAB-receptor activation partially restores network dysfunction associated with NMDA-receptor hypofunction

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Cognitive deficits and impaired sensory processing are hallmarks of neurodevelopmental and neuropsychiatric disorders, such as schizophrenia and autism. N-Methyl-d-aspartate receptor (NMDAR) hypofunction is considered to be involved in causing these deficits by disrupting excitation-to-inhibition balance in neuronal circuits. Activation of GABAB-receptor is hypothesized to restore this imbalance, but its effect on translational electrophysiological biomarkers is poorly understood.

Here we studied the physiology of limbic-auditory circuits under pharmacological NMDAR blockade (using MK-801) and GABABR activation (using Baclofen) in freely-moving rats, implanted with electrodes in key brain areas. The pharmacological effects were assed on several translational readouts from resting-state EEG, auditory-evoked oscillations and mismatch-negativity paradigms, evaluated through power spectral, coherence and event-related estimates.

Across brain areas, MK-801 increased the power of both spontaneous and auditory-evoked brain oscillations, mainly in the gamma and higher frequency range. Baclofen partially normalized this aberrant oscillatory activity. Furthermore, coherence analysis indicated that functional coupling in auditory-limbic circuits is substantially altered by MK-801, such as increased coupling of the frontal cortex with the auditory cortex and the amygdala in the theta band. For higher frequency bands (e.g. high gamma), coherence was increased in a network comprising frontal cortical regions and thalamic nuclei. Baclofen normalized coherence between frontal cortex and amygdala and augmented the MK-801 induced increase of gamma coherence in thalamic and thalamocortical circuits. Additionally, we found clear deficits in auditory mismatch responses under MK-801, involving both prediction error and adaptation components across limbic-auditory brain regions. Baclofen did not restore these deficits but even impaired mismatch responses when applied alone.

GABABR activation partially restores oscillatory changes associated with NMDAR-hypofunction, but had a detrimental effect on functional coupling and context-dependent auditory processing. Our results indicate that GABABR agonists may be of limited therapeutic value for neurodevelopmental disorders associated with NMDAR hypofunction.

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PS3-75

Deciphering the molecular mechanism of Plk1 control of adult neural stem cell activation, self-renewal and differentiation

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Adult neural stem cells (NSCs) dwell in specialized microenvironments called niches, being the most studied the subependymal zone along the lateral ventricles, and the subgranular zone of the dentate gyrus. Despite being mainly quiescent, NSCs can be transiently activated by specific signals, so they can proliferate but also re-enter a state of inactivation to avoid exhaustion. The total pool of NSCs at a given time point is a consequence of NSC decision-making throughout their life-span transiting through 'maintenance', by the active regulation of quiescence and the self-renewing asymmetric divisions of activated NSCs; 'reduction', by terminal, symmetric or asymmetric differentiation; or 'expansion' due to self-renewing symmetric divisions. Whether the instructions that guide the making of these decisions are determined by intrinsic properties, by the microenvironment of the niche or a combination of signals is the subject of intense investigation. Data from our group indicate that Plk1 is a novel intrinsic regulator of adult neurogenesis. In an effort to unravel the molecular mechanism by which this control is attained, we have found a link between Plk1 and a master regulator of neurogenesis, through which we propose Plk1 controls activation, the mode of division and differentiation of NSC towards the neuronal lineage.

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PS3-76

New experimental models for the study of Friedreich's Ataxia

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Friedreich's ataxia (FRDA) is a rare autosomal recessive neurodegenerative disease. Although is a systemic disease, spinal cord and cerebellum are among the most severely affected tissues. Gait instability, loss of coordination in arms and legs or dysarthria are some of the hallmarks of the disease with most of the cases detected during the childhood. At a molecular level, FRDA is mainly caused by a GAA triplet repeat expansion in the first intron of the gene codifying for frataxin (FXN), leading to a decreased expression of this mitochondrial protein. One of the main challenges for the study of FRDA is the absence of good experimental models that mimic the human disease, likely due to the difficulty to recreate the pathological expansion. New models are currently emerging in order to better understand the physiopathology of the disease and test for therapeutic approaches. Thus we have characterized two experimental models which bear the human frataxin gene with a pathological expansion. As a cellular model, we have generated induced FRDA neurons by direct reprogramming from adult human fibroblasts. Furthermore we have characterized a new humanized mouse model harbouring a human frataxin gene with a >800 GAA repeat expansion (www.jax.org/strain/030395), herein referred to as YG8JR, and some of their neuronal populations in culture. In comparison to control conditions, induced FRDA neurons and neuronal cells cultured from the YG8JR mouse show low levels in FXN leading to modifications in the mitochondrial network pattern as well as in the complexes of the mitochondrial electron transport chain. Moreover, the YG8JR mouse model show an ataxic phenotype, with a decline in motor tests, such as rotarod, severe loss of weight, atrophy of the cerebellum, loss of neuronal cells and synaptic alterations. Overall, we think these new models will help to gain a better knowledge of the disease and may be helpful for drug screening to treat the disease.

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PS3-77

Tauroursodeoxycholic acid supports early functional recovery of rats with spinal cord injury but does not improve effects of transplanted bone marrow-derived stromal cells

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Background: Tauroursodeoxycholic acid (TUDCA) is a bile acid with anti-inflammatory effects on microglia and macrophages. Implants of bone marrow-derived stromal cells (bmSC) are currently under investigation in clinical trials of spinal cord injury (SCI). We studied the therapeutic effect of TUDCA and a combinatorial treatment with human bmSC in a rat model of SCI.

Methods: Spinal cord contusion injury was induced at thoracic level T9. Treatment consisted of two injections of 100 mg/kg TUDCA, immediately after lesion and at 1 dpo, combined with one sub-occipital injection of human bmSC into the cisterna magna. Control groups received injections of saline or TUDCA treatment only. The recovery of motor functions was assessed during a surveillance period of six weeks. Rats were sacrificed after 4 days for biochemical and histological investigation or after 6 weeks for histology of the tissue.

Outcome: Treatment with TUDCA improved the recovery of autonomic bladder control and had a positive effect on motor functions in the subacute phase. Biochemical analysis of spinal cord tissue confirmed its anti-inflammatory activity. Effects on motor function were only transient, however, such that no significant differences between vehicle and TUDCA-treated animals were observed 1-6 weeks after lesion. Combinatorial treatment with TUDCA and bmSC failed to have an additional effect compared to treatment with bmSC only.

Keywords: bile acid, spinal cord injury, stromal cells, rat

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PS3-78

NEUROPROTECTIVE EFFECT OF REMOTE ISCHEMIC PERCONDITIONING AND POSTCONDITIONING IN A PRECLINICAL MOUSE MODEL OF ACUTE ISCHEMIC STROKE

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Remote ischemic conditioning (RIC) is an endogenous procedure that reduces ischaemic injury by repeated transient mechanical obstruction of vessels at a remote limb from the injury site. It represents a new paradigm in neuroprotection with unknown mechanism of action. This study aimed to evaluate the neuroprotective effect of per-RIC (during ischemia) and post-RIC (after ischemia) in a preclinical mouse model of acute ischemic stroke.

A mouse model of transient focal cerebral ischemia by compressing the distal middle cerebral artery (tMCAO) for 60 min was used. Animals were classified into three groups: MCAO group, per-RIC group (during MCAO) and post-RIC group (10 minutes after MCAO). RIC consisted of 3 x 5 min cycles of right hind limb ischemia. Infarct volume, functional neurological score and histological examination were evaluated 72h after reperfusion. Multiple inflammatory cytokines in the peripheral blood were measured using a Multiplex Assay. Light-sheet fluorescence microscopy technique was used to determine the effects of RIC on the microvascular network.

Per-RIC (n=10) and post-RIC (n=10) significantly reduced the infarction size 3 days after reperfusion compared to the group that did not receive RIC (n=10). In addition, RIC treatments significantly improve the neurological outcome and shown specific cellular pattern and morphological profile in the peri-infarct region. MCAO had a specific cytokine profile with a peak of inflammatory expression at 6 hours post stroke. RIC treatments shown a specific time-dependent cytokine profile. Per-RIC significantly increased the expression of both proinflammatory (GM-CSF) and anti-inflammatory cytokines (IL-10 and IL-13) at 6h, while Post-RIC significantly decreased the levels of proinflammatory cytokines (IL-6 and IL-12p70) and chemokine (KC). In addition, RIC strategies had different effect on the brain vasculature determined by a quantitative analysis of estimated density and vessel diameter.

Our results suggest that per-RIC and post-RIC may be used as a novel neuroprotective strategy against ischemia injury. Both strategies showed neuroprotective role but distinct signalling pathways.

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PS3-79

ROLE OF THE IMPRINTED GENE CDKN1C IN THE DIFFERENTIATION PROCESS OF NEURAL STEM CELLS

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Neurogenesis throughout adult life is supported by multipotent neural stem cells (NSCs), characterized by their abilities of self-renewal and differentiation into the three different neural lineages: neurons, astrocytes and oligodendrocytes. Both capabilities are maintained by specific intracellular mechanisms that are activated by extracellular signaling from the microenvironment or niche in which they reside in vivo, the subventricular zone (SVZ) and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. Genomic imprinting is an epigenetic process that causes genes to be expressed depending on their parental origin, causing a monoallelic expression of a subset of genes called imprinted genes. This process is implicated in the control of gene dosage in the neurogenic niches. Cyclin-dependent kinase inhibitor 1C (Cdkn1c) is an imprinted gene expressed by the maternal allele and encodes the P57 protein that plays a crucial role during development of cerebral cortex and also in the maintenance of quiescence in NSCs from the SGZ. Alterations in Cdkn1c expression have implications in neurological syndromes such as Beckwith-Wiedemann or Prader-Willi. However, it is not known the role of P57 in the neurogenesis process. This work characterizes the expression of the imprinted gene Cdkn1c and its coding protein P57 in the adult SVZ, showing that P57 is present in GFAP+ cells located close to the lateral ventricles and in differentiated cells, suggesting an important role of P57 at differentiation process. We also evaluate the role of P57 in adult SVZ NSCs quiescence and differentiation by in vivo electroporation of NSCs in a Cdkn1c-deficient murine model, showing that P57 is involved in terminal differentiation of NSCs into glial linages.

PS3-80

An in vivo reprogramming model to study glioblastoma formation

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Glioblastoma multiforme (GBM) is the most frequent and aggressive primary tumour developing in the Central Nervous System. Within GBM, a group of cells with stem cell features has been described, the glioma stem cells (GSCs). GSCs have the potential to give rise to a complete GBM by themselves and have been postulated to be responsible for the origin of the tumour. In the adult mammalian brain, a pool of multipotent neural stem cells (NSCs) with the ability to self-renew and give rise to differentiated neural lineages is maintained throughout life. NSCs share several features with GSCs, making them excellent candidates for being the origin of GBM. Our group has developed a murine model of GBM formation based on the in vivo reprogramming of NSCs in the adult brain. These mice carry a polycistronic cassette encoding Yamanaka's factors (Oct4, Sox2, Klf4 and c-Myc), specifically induced in glial fibrillary acidic protein (GFAP) cells after doxycycline administration. Our results show that GFAP+ cells, when reprogrammed, are capable of giving rise to tumoral masses in the brain with high efficiency, some of them sharing many features with GBM. We have also traced the origin of these tumours specifically targeting quiescent NSCs (qNSCs) by in vivo electroporation and found that qNSCs are one of the possible cells of origin of GBM.

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PS3-81

Comparing astroglial reactivity in two transgenic mouse models of tauopathy

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Astrocytes are becoming crucial players in the pathology of neurodegenerative disorders, such as Alzheimer's disease (AD). Astrocyte responses have been mainly analyzed in the context of amyloid-beta (Abeta) pathology, highlighting their role in the development/progression of amyloidosis and their relationship with the microglial response. Regarding tau pathology, some studies have reported that astrocytes respond to hyperphosphorylated tau (phospho-tau) and suggested their implication on tau transmission/elimination. Here, we aimed to analyze the astroglial reactivity to tau pathology in the hippocampus of two transgenic mouse models of tauopathy, ThyTau22 and P301S. Proteinopathy was assessed by western-blotting and immunohistochemistry using phospho-tau antibodies (AT8). Inflammatory markers (GFAP, Iba-1, CD45, TREM2) were analyzed by qPCR and immunohistochemistry for bright-field microscopy; glial-phospho-tau relationship was analyzed under confocal and transmission electron microscopy. P301S mice exhibited an intense reactive astrogliosis, increasing with aging in parallel to a strong phospho-tau pathology. ThyTau22 model showed a slighter astrocyte reactivity accompanied by a lesser accumulation of phospho-tau. Astrogliosis in P301S mice closely correlated with an acute DAM-like microglial activation, not observed in ThyTau22 hippocampus. Confocal and ultrastructural studies revealed that, in both models, astrocytic processes contained phospho-tau, especially those surrounding blood vessels. Our results support that astrocytes respond to tau pathology in the absence of Abeta. This reactivity highly correlates with phospho-tau pathology and markedly depends on microglial activation. Moreover, astrocytes may play a role in the elimination/spreading of phospho-tau species through the brain. Deciphering the mechanisms underlying these processes might help to develop therapies to slow down the progression of AD.

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PS3-82

COMBINED CELL AND GENE THERAPIES STOP MITRAL CELL DEATH IN PCD MICE

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The Purkinje Cell Degeneration (PCD) mutant mouse suffers the postnatal death of the mitral cells of the olfactory bulb. Previous results demonstrated that a transplant of healthy bone marrow slows down the degeneration of these neurons, improving the olfaction of PCD mice. Besides, IGF1 is a growth factor with neuroprotective properties that is also defective in PCD mice. Then, we combined both cell and gene therapies by over-expressing the Igf1 gene in transplanted cells for optimizing the neuroprotection for PCD's bulbar degeneration.

Hematopoietic stem cells from healthy green fluorescent protein (GFP) donors were cultured during 9 days in vitro (DIV). At DIV 7, the cells were infected with lentiviruses carrying the Igf1 gene under the EF1a constitutive promoter, and the cyan fluorescent protein (CFP) as reporter molecule. In parallel, the bone marrow of PCD mice was ablated by an irradiation of 7.5 Gy at postnatal day 19 (P19). At P20, irradiated animals received an intravenous transplant of 7.5 million of unfractioned healthy bone marrow stem cells, supplemented with genetically modified hematopoietic cells (ratio 1:1). At P150, animals were sacrificed and their olfactory bulbs were analyzed by immunofluorescence techniques and quantitative PCR.

Our results showed that the transplantation of a genetically modified healthy bone marrow virtually stopped the mitral cell loss of PCD mice. Interestingly, it also allowed the survival of certain Purkinje cells, a practically inexistent neuronal population in PCD mice at P150. Both standard and genetically modified transplants activated PCD's microglia also changing its inflammatory pattern, which resembled a wild-type one. Additionally, the genetically modified transplant prevented DNA damage, which seems to be the most plausible mechanism that underlies its higher protection. Therefore, the combination of cell and gene therapy supposes a remarkable strategy to achieve neuroprotection.

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PS3-83

WHY THE LOBULE X OF THE CEREBELLUM RESISTS THE NEURODEGENERATION OF THE PCD MOUSE?

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The Purkinje Cell Degeneration (PCD) mouse suffers a mutation in the Ccp1 gene, which codifies a carboxypeptidase responsible for the stability of the cytoskeleton. Under its absence in the PCD mouse, the Purkinje cells (PC) of the cerebellum collapse and at 30 post-natal days (P30) just a few PC remain alive, mainly in the lobule X. It is not fully understood why this region maintains its cell population longer than the other lobules.

We have studied several genes related with Ccp1 and the equilibrium of the cytoskeleton, like Ccp4, Ccp6 and Ttll1 by qPCR and by Western Blot; the Ccp family deglutamylates the cytoskeleton, the Ttll family polyglutamylates it, and both families must stay in equilibrium. Besides, we have studied with immunohistochemistry techniques the expression of HSP25, a Heat-Shock-Protein responsible for the neuroresistance of the lobule X in other animal models of ataxia. Moreover, we have also analysed the expression of the phosphorylated version of HSP25 (HSP25-P), which has even more anti-apoptotic properties.

We demonstrated that the lobule X of the wild type cerebellum has a lower expression of Ccp1, so it is possible that this lobule is less dependent of this gene, its absence being less harmful in the PCD mouse. Similarly, Ttll1 is less expressed in the lobule X than in the rest of the vermis, which could imply that the cytoskeleton of this lobule is less glutamylated, so that is why the deglutamylating function of Ccp1 is less required. Finally, we have seen that both HSP25 and HSP25-P are more expressed in the lobule X of the PCD mouse than in the wild type one. Therefore, HSP25 and HSP25-P could be also responsible of the neuroresistance of the lobule X in the PCD mouse. Altogether our data suggest a multifactorial origin for the neuroresistance of this cerebellar region.

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PS3-84

Natural IgMs that bind to the neo-epitopes present in corpora amylacea of the human brain recognize carbohydrate structures

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Corpora amylacea (CA) are spherical polyglucosan bodies that accumulate primarily in the periventricular, perivascular and subpial regions of the human brain during aging and some neurodegenerative diseases. Recent studies indicate that CA gather waste substances from the brain and act as waste containers. It has been reported that CA contain some neo-epitopes (NEs) recognized by natural IgMs, but these NEs are still undefined. Here, we performed IgM preadsorptions with increasing concentrations of specific monosaccharides to find out if the preadsorption produced a partial or total inhibition of CA staining by the IgMs. As controls, the same studies were performed by staining CA with concanavalin A (ConA), a plant lectin that binds to particular carbohydrate structures, and with an antibody directed against the p62 protein (anti-p62). ConA and anti-p62 were preadsorbed with the mentioned monosaccharides under the same conditions as IgMs. As expected, CA staining with ConA was blocked by the preadsorption with the appropriate monosaccharides. On the other hand, CA staining with anti-p62 was not affected by any monosaccharide tested, which demonstrated that the preadsorption with the sugars did not block the antibodies directed against the proteins. Regarding IgMs, we observed that the binding between the natural IgMs and the NEs sited on CA become interfered in vitro by the preadsorption with certain monosaccharides, particularly by glucose. These findings point out the carbohydrate nature of the NEs located in CA. Moreover, the present study indicates that, in vitro, the binding between certain natural IgMs and certain epitopes may be disrupted by some monosaccharides. Whether these inhibitions may also occur in vivo will be addressed in future experiments. In this regard, further studies will be carried out to assess the possible in vivo effect of glycemia on the reactivity of natural IgMs and, by extension, on natural immunity.

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PS3-85

Neo-epitopes from corpora amylacea in the human brain do not have a peptidic nature

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Aging and neurodegenerative processes induce the formation of waste substances in the brain. Some of these substances accumulate in corpora amylacea (CA), a type of polyglucosan bodies constituted primarily by polymerized hexoses. CA act as waste containers, since they contain waste products from the human brain, are released from the brain into the cerebrospinal fluid, and reach the cervical lymph nodes where they are phagocytosed. In recent work, we found out that CA contain some neo-epitopes (NEs) that are recognized by natural IgMs, revealing a possible link between them and natural immunity. Natural antibodies, always present in the blood, help to maintain homeostasis by interacting with the NEs formed in old or damaged structures. Although some of these NEs are of carbohydrate nature, the precise nature of the NEs contained in CA is still unknown. In order to shed light on their nature and to discard that they are of peptidic nature, we stained the CA with IgMs after their digestion with pepsin. As controls, digested CA were stained with an antibody directed against the p62 protein (anti-p62), with an NHS ester probe, which binds to proteins, and with concanavalin A (ConA), a carbohydrate-binding protein. Predictably, the digestion of CA proteins prevented the CA staining with both anti-p62 and NHS ester probe, but the staining with ConA, which is directed against sugar structures instead of proteins, was unaltered. Similarly, CA staining with IgM was maintained after pepsin treatment. This evidence consistently rejects the protein nature of the NEs sited on CA while supports their carbohydrate nature. Moreover, the possible presence of carbohydrate NEs in CA reinforces that CA are structures involved in the entrapment of damaged and non-degradable products and their role in protective or cleaning mechanisms.

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PS3-86

INSULIN-LIKE GROWTH FACTOR I COUPLES METABOLISM WITH CIRCADIAN ACTIVITY THROUGH HYPOTHALAMIC OREXIN NEURONS

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Uncoupling of metabolism from circadian activity is associated with increased risk of various pathologies, including neurodegeneration. Recently, insulin and the closely related insulin-like growth factor I (IGF-I) were shown to entrain feeding patterns with circadian rhythms. Moreover, both hormones act centrally to modulate peripheral glucose metabolism; however, whereas central targets of insulin actions are intensely scrutinized, those mediating the actions of IGF-I remain undefined. We analyzed whether IGF-I targets orexin neurons in the lateral hypothalamus, as these neurons are involved in circadian rhythms and energy allocation, and are modulated by IGF-I. Mice with disrupted IGF-IR activity in orexin neurons show phase shifts in circadian feeding behavior, loss of circadian orexin expression, and gradually develop sex-dependent metabolic alterations. We also found that central modulation by IGF-I of hepatic KLF transcription factors involved in peripheral glucose metabolism is mediated by orexin neurons. Thus, IGF-I entrains energy metabolism and circadian rhythms through hypothalamic orexin neurons.

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PS3-87

DESIGN AND IMPLEMENTATION OF A METHOD TO STUDY LARYNGEAL RESISTANCE DURING THE STIMULATION OF CUNEIFORM NUCLEUS (CnF) IN SPONTANEOUSLY BREATHING ANAESTHETIZED RATS

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Background: abduction and adduction of the vocal folds are performed by motoneurons located in the loose formation of the nucleus Ambiguus (nA) innervating the laryngeal muscles. In previous studies we have demonstrated a functional interaction between hypothalamic (DMH-PeF), mesencephalic (dlPAG) and pontine nuclei (PBc, A5 region) involved in cardiorespiratory control and in changes of laryngeal caliber (López-González et al., 2020; Lara et al., 2002). The Cuneifom nucleus (CnF) of the mesencephalon has afferent and efferent connections with all these nuclei. The aim of this study was to characterize the electrophysiological relationships between the CnF and those pontine-medullary neuronal circuits to understand their role in laryngeal control and its effect on vocalization. To achieve this objective is necessary to develop a variation of the classical technique of the "isolated glottis in situ" for the recording of subglottic pressure in rats.

Methods: experimental basic preclinical study in non-inbred male rats [SPF, Sprague-Dawley (250-300 grams)]. Animals were anesthetized with sodium pentobarbitone (60 mg/kg i.p., initial dose, supplemented 2 mg/ kg, i.v., as necessary). A double tracheal (upwards for the "glottis isolated in situ" technique, and downwards in the direction of the carina). Vagus and laryngeal recurrent nerves were isolated and stimulated with bipolar electrodes (Ag/AgCl). Electrical stimulation of the CnF using concentric bipolar electrodes was performed (1 ms pulses, 20-40 µA, 100 Hz for 5 s). Subglottic pressure, respiratory flow, pleural pressure, blood pressure, heart rate and unitary neuronal activity were also recorded.

Results: subglottic pressure was recorded in rats with an aneroid transducer (ADInstrument model FE141, ± 0,03 psi) by passing a stream of humidified medical air upwards through the larynx at a constant rate of 50-100 ml/min with a thermal mass digital air flow meter controller (Bronkhorst Hi-Tec F-201CV-AGD-22-V)

Conclusions: our variation of the classical technique for the recording of the "isolated glottis in situ" in rats shows good dynamic responses and can be perfectly used as an index of subglottic pressure and laryngeal activity.

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PS3-88

Imaging of synapses in 3D with non-destructive synchrotron X-ray ptychography

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Wiring diagrams of neural circuits are of central importance in delineating mechanisms of computation in the brain. Hereby, the individual parts of neurons - axons, dendrites and synapses - need to be densely identified in 3-dimensional volumes of neuronal tissue. This is typically achieved by volume electron microscopy, which requires ultrathin physical sectioning or ablation, using high precision slicing techniques or ion beams, either before or during the image acquisition process.

Here, we employed cryogenic X-ray ptychographic tomography, a coherent diffractive X-ray imaging technique, to acquire 3-dimensional images of metal-stained mouse neuronal tissues with sufficient resolution to densely resolve axon bundles, boutons, dendrites and synapses without physical sectioning.

We show that a tissue volume of 10-20 µm in diameter can be imaged with X-ray ptychographic tomography and subsequently with focussed ion beam-scanning electron microscopy (FIB-SEM). This suggests that metal-stained neuronal tissue can be highly radiation-stable. Using FIB-SEM as ground truth, we show that X-ray ptychographic tomography resolves 60% of the synaptic contacts in the mouse olfactory bulb external plexiform layer with an 80% precision.

We demonstrate that synapses can be detected using X-rays. Ongoing improvements in synchrotron, X-ray and detector technologies as well as further optimization of sample preparation and staining procedures could lead to substantial improvements in acquisition speed. Combined with laminography and nano-holotomography it could allow for non-destructive X-ray imaging of synapses and neural circuits in increasingly larger volumes.

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PS3-89

Obtention and characterization of exosomes for non-invasive epilepsy monitoring

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Exosomes are a type of small (30-200 nm) extracellular vesicles, which have a single membrane and a cytosol filled with proteins, DNA, RNA and other molecules. These vesicles play a fundamental role in intercellular communication, since they are synthesized by all types of cells and can transport molecules, even changing the phenotype of a receptor cell to a phenotype similar to the cell that has synthesized the vesicle. Such is their importance that they have already been related to several biological processes such as homeostasis, angiogenesis or the immune response; and to several pathologies such as cancer, neurodegenerative diseases and epilepsy. The aim of this project has been to perfect a method for isolating and characterization of blood exosomes from the GASH/Sal model of epilepsy using different techniques. The GASH/Sal constitutes an experimental model of reflex epilepsy of audiogenic origin derived from an autosomal recessive disorder. Differential centrifugation and size exclusion chromatography were the two isolation techniques chosen for this project and those that allowed the isolation of exosomes from GASH/Sal hamsters. Regarding the characterization techniques, electron microscopy and Nanosight particle tracker were useful to characterize the size and concentration of exosomes. We obtained particles ranging in diameter from 50 to 180 nm and a concentration of 1.8-2 x 108 particles/ml. However, flow cytometry and western blotting did not identified exosomes in the samples, because commercial antibodies against CD63, one of the exosomal typical markers, did not work for Syrian hamster. Future challenges should focus on designing these types of antibodies and, above all, on analyzing the content of the exosomes to find molecules that may be related to epilepsy.
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PS3-90

GENE THERAPY WITH VMAT2 REDUCES AGE-DEPENDENT NEUROMELANIN ACCUMULATION AND PREVENTS PARKINSON'S DISEASE PHENOTYPE IN NEUROMELANIN-PRODUCING RATS

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In Parkinson's disease (PD), there is a preferential degeneration of neurons that contain the pigment neuromelanin, especially dopaminergic neurons of the substantia nigra (SN), the loss of which leads to classical motor PD symptoms. 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. Because neuromelanin derives from the oxidation of free cytosolic dopamine, we hypothesized that enhancing dopamine vesicular encapsulation with vesicular monoamine transporter 2 (VMAT2) will decrease cytosolic dopamine that can convert to neuromelanin. This approach should slow down the intracellular buildup of neuromelanin that occurs with age and thus prevent, delay or attenuate PD pathology.

Adult male Sprague-Dawley rats received single unilateral stereotaxic co-injections of AAV-hTyr and AAV-VMAT2 immediately above the SN. Control animals received equivalent amounts of either vehicle, AAV-hTyr or AAV-VMAT2, separately. At selected times post-injection animals were assessed for motor asymmetry and their brains processed for histological analyses.

VMAT2 overexpression in hTyr-expressing rats reduced intracellular neuromelanin to levels below its pathogenic threshold by lowering the production of dopamine-oxidized neuromelanin precursors. In these animals, reduction of neuromelanin levels was associated with a marked attenuation of Lewy body-like inclusion formation, nigrostriatal degeneration, extracellular neuromelanin accumulation, microglia/macrophage activation and PD-like motor deficits.

Our results demonstrate the feasibility and therapeutic potential of modulating intracellular neuromelanin levels in vivo.

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PS3-91

Age-related changes in the neuromuscular junction and skeletal muscle of C57BL/6J mice

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Aging is accompanied by a reduction of muscle mass and strength, known as sarcopenia, and an important impairment of motor abilities.

To elucidate mechanisms leading to sarcopenia, we undertook a detailed characterization of pathophysiological changes occurring in the mouse neuromuscular system over the course of aging. Motor behavioral and electrophysiological tests, and histological and immunocytochemical analyses were performed in slow- and fast-twitch muscles of young, adult and old C57BL/6J mice. Aging was associated with a reduction in body weight and a gradual decline in locomotor activity of mice. In muscles from old mice, neuromuscular junctions showed higher numbers of both polyinnervated and denervated endplates, signs of endplate fragmentation and ectopically innervated acetylcholine receptor clusters throughout myofibers. In relation to adult animals, skeletal muscles of old mice exhibited increased expression of different molecules related to neuromuscular junction stabilization and plasticity, including: CGRP, GAP-43, FGBP1, TGF-β1 and agrin. Moreover, a higher proportion of myofibers showing increased size, central nuclei (indicating a process of degeneration and regeneration), and lipofuscin aggregates were found in muscles from old mice when compared with those in adult animals. Changes in fiber type composition, a decrease in the number of satellite cells and a reduction of both PGC-1α and ATP5A in old muscles were also found. In relation to young-adult mice, old animals had a significant reduction in the nerve conduction velocity and the amplitude of the compound muscle action potential in distal plantar muscles. Although the distinct type of old muscles examined share some common features indicative of the aging process, the profile of some alterations differed between muscles. This variability was noticed even between muscles located in close vicinity and having similar type composition. These data suggest that the degree of activity and specific function of muscles, rather than topography and fiber typology, have greater impact on muscular changes occurring with aging.

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PS3-92

Developmental neurotoxicity effects of nanoplastics in zebrafish embryo and human neural stem cell models

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Plastic production has increased exponentially and a significant proportion ends up in aquatic and terrestrial environments. Mechanical, physical, and biological processes degrade this material producing micro (< 5 mm) and nanoplastics (< 1000 nm; NP). Exposure routes include ingestion (food and water), inhalation, and dermal absorption. In addition, microplastics have recently been discovered in human placentas. Some NP health effects have been reported, and developmental neurotoxicity (DNT) is one of the most important ones due to the smallest NP potential capacity to penetrate the blood-brain barrier. Therefore, our main objective was to investigate possible DNT effects of NP at a cellular and organism level.

To accomplish this, we selected an in vivo model, the developing zebrafish embryo, and an in vitro model, a human neural stem cell line, both widely used to study DNT. The two models were exposed to polystyrene NP of 30 nm, fluorescently labeled and pristine, at concentrations that have been reported in nature, ranging from 0,2 - 10 mg/L. Embryos were exposed from 1 - 120 hours post-fertilization, and cells for a total of 16 h - 4 days.

Our results show that 30 nm NP can penetrate both embryo and cell models but are not able to enter the cell nuclei. Accumulation was dependent on concentration. Developing neural cells suffered from morphological changes that were reflected in proliferation and differentiation markers, and increased mortality. NP particles penetrated zebrafish organs, blood vessels, and were observed in larvae brain, eyes, and otoliths. DNT was indicated by smaller head and eye sizes, and alterations in locomotion, anxiety, and acetylcholinesterase assays.

In conclusion, 30 nm polystyrene NP are able to accumulate in cells and organs and induce DNT effects in both in vitro and in vivo models.

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PS3-93

Brief assessment of social cognition in "ataxia da Costa da Morte"

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SCA36 is a late-onset spinocerebellar ataxia affecting families from Costa da Morte (Galicia, Spain). It presents manifestatations consistent with the presence of cerebellar cognitive-affective syndrome. However, social cognition has not been evaluated in these patients. We used the “Reading Mind in the Eyes” Test in 21 patients of different stages of disease, matched in age, sex and educational level with 21 controls. Emotional processing of human faces, specifically those with negative and neutral valence, seems to be altered in preataxic stage, before first motor symptoms. Nevertheless, correct answers to negative stimuli continue decreasing as the disease progresses and correlate with the motor impairment measured with the SARA scale. This result supports the hypothesis that the change in the recognition of social emotions could be specifically related to an alteration in the cortico-cerebellar circuit.

PS3-94

Aging effects on emotional regulation are supported by differential neural networks as predicted by machine learning paradigms

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Aging is one of the primary health concerns in the entire world. Healthy seniors experience a cognitive decline that affects their daily functioning, yet their ability to process emotional information seems to be well-preserved. Aging modulations on this cognitive-emotional interrelation as well as the underlying neural networks remain unclear. Hence, we aimed to examine the neural underpinnings of joint emotional and memory processing in young and older individuals with electroencephalography (EEG). To this end, 34 young and 38 older individuals performed an memory task with emotional content while they were recorded with a 128-channel EEG system. Specifically, they performed an emotional recognition task with positive, negative and neutral pictures. Behavioural data was analysed under the frame of the Signal Detection Theory. We employed EEG machine learning paradigms to gain insight into the neural data. Specifically, we used linear (logistic regression) and nonlinear (multi-layer perceptrons) automatic models in order to classify subjects by age, just considering the neural information collected by EEG. Behavioural results reflect that older adults exhibit a reduced recognition ability for positive stimuli compared to young adults, suggesting that positive stimuli may generate higher interference than negative or neutral stimuli in emotional recognition with age. EEG results indicate that neural information alone can successfully classify young and older participants with high accuracy. In this regard, we are currently running brain-behavioural correlations that may help us fine-tune the interpretation of these results.

Key words: aging, cognitive-emotional interrelation, emotional recognition task, EEG, machine learning paradigms

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Functional and morphological study of transient ischemia-reperfusion in adult pigmented mice

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Purpose: Transient ischemia-reperfusion (I/R) induced by acute elevation of the intraocular pressure (IOP) is a commonly employed method to study acute angle-closure glaucoma. Here, we assess various ischemic and survival intervals with functional and histological techniques.

Methods: I/R was induced in C57BL/6J mice by inserting a 30G needle in the anterior chamber of the left eye connected to a 500mL bottle of 0.9%NaCl at a high of 150cm, to increase the IOP from 8 to ≈90 mmHg. Four intervals of ischemia were studied (45', 60', 75' or 90') (n=4 each group) and 3 days later mice were perfused, their retinas flat-mounted and immunolabelled against Brn3a to identify retinal ganglion cells (RGCs). We also studied the effects of 60' I/R: in vivo retinal function by electroretinograms recordings at 3, 7, 14, and 21 days after injury (n=12) and ex vivo the survival of several retinal populations at 3, 7, 14 or 21 days, including RGCs, horizontal cells and S-cone and L/M cone photoreceptors; identified with Brn3a, calbindin, S- and L/M-Opsin antibodies, respectively.

Results: At 3 days of 45' of I/R the Brn3a+RGC population remained intact, however after 60', 75' or 90' the Brn3a+RGC population it was reduced to 75, 37.5 and 12.5 percent, respectively. At 7 days after 60' of I/R, Brn3a+RGCs decreased to 50%, and remained unchanged at 21 days. Horizontal cells and S-cones remained unchanged at every time interval examined. L/M cones diminished significantly at 7 days (≈70%) and further decreased to 58% at 14 days without further changes at 21 days. Functional analysis shows a permanent decrease in all waves studied, from 3 to 21 days after I/R.

Conclusions: Pigmented mice retina shows a damage threshold between 45' and 60' minutes of I/R for RGC survival. 60' of I/R leads to a rapid loss of innermost retina that from 3 to 7 days, the horizontal cells are not affected, while in the outer retina, L/M cones are affected but S cones are not.