Poster Session 4: Friday, 5th November, from 09:00 to 12:30, Exhibition Hall.

PS4-01

Dispersion and fate of pallial progenitors within the adult forebrain

Edwards Antonio Cabrera[1], Rebeca Sánchez-González[1,2], Ana Cristina Ojalvo-Sanz[1,2], Sonsoles Barriola[1,2], Laura López Mascaraque[1]

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NG2-glia, also named as NG2-cells, is a neural cell type with a particular morphology and function different to neurons, astrocytes, and oligodendrocytes. Classically NG2-glia were considered as precursor of oligodendrocyte cells (OPC) but those cells have many different roles from development to adulthood, besides to be involved in the response to brain injury. In addition, this neural cell population persists in the adult brain, where they comprise about 5-8% of all CNS cells, and distribute homogenously throughout grey and white matter. NG2-glia is a highly proliferative cell population in both during development and adulthood, suggested that they are not just lineage-committed progenitors, but also multipotent neural stem cells. To decipher in vivo the adult cell potential of NG2 progeny of single E16 progenitors, we performed a novel variant of the StarTrack, the NG2-StarTrack, which expression is drived by the mouse NG2 promoter. NG2-StarTrack plasmids and the hyPBase transposase were injected intracerebroventricular lateral of embryos mice and the E16-progenitors of the dorsal wall transfected by electroporation. At P250 we performed a morphological and immunohistochemical analysis of the derived NG2-cell progeny from E16-progenitors, to assess the progenitor cell fate at late adult ages. We identified StarTrack labeled cells with several neural phenotypes in different regions of the forebrain, as interneurons in the granule cell layer of the olfactory bulb. In addition, in the somatosensory cortex labeled cells showed diverse morphologies corresponding to oligodendrocytes, protoplasmic astrocytes, pial astrocytes, NG2-glia, and even neurons. In the corpus callosum, NG2-StarTrack labeled cells displayed cell phenotypes with a morphological and immunohistochemical features of oligodendrocytes, fibrous astrocytes, and NG2-glia. Together, this specific in vivo targeting of embryonic neural progenitors reveals new data on the cell fate of the heterogeneous pool of single E16 dorsal progenitors. Supported by research Grants from MICINN (PID2019-105218RB-I00) and Fundación Ramón Areces (Ref. CIVP9A5928). EAC is supported by CONACyT number 770752.

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PS4-02

Perturbation of adherens junctions associated proteins in the neocortex affects neurodevelopmental pathways causing cognitive and social deficits in mice

Mr. David de Agustín-Durán[1], Ms. Alba Marín-Garnes[1], Ms. Ana Pérez-Villalba[2], Ms. Isabel Mateos-White[1], Mr. Jaime Fabra-Beser[1], Dra. Cristina Gil-Sanz[1]

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The neocortex accomplishes a wide range of sophisticated tasks, such as cognition, language, sensory perception and motor integration. In order to conduct them, the neocortex displays an extensive cell diversity arisen from neural stem cells, known as radial glial cells (RGCs), through tightly regulated mechanisms. In particular, RGCs lining the ventricular walls produce different subsets of excitatory projection neurons (PNs) distributed in a laminar manner with specific molecular signatures, morphologies and connection patterns. Among them, cortico-cortical PNs, mostly located within the upper cortical layers, are increased in superior mammals like primates and are described to be more susceptible to dysfunction in psychiatric disorders. Previous studies have shown that genetic inactivation of adherens junction (AJ)-associated proteins Cdh2 and afadin in the dorsal telencephalon, produces dramatic expansion of the neocortex due to the overproduction of PNs expressing upper-layer neurons markers. These features have been detected in certain rodent models of autism spectrum disorder (ASD) as well as in some ASD patients. Here, we aim to understand the molecular mechanisms acting downstream of these AJ-associated proteins involved in the control of neocortical progenitor behaviour and how alterations in these genes could cause cognitive and social deficits like the observed in ASD patients. To this end, we have examined the expression of candidate genes by RT-qPCR in these conditional AJs mutant mice and found changes in some genes whose dysregulation has been also linked with ASD. In order to unveil the existence of cognitive and social alterations in these mice, we have performed a thorough behavioural characterization. Taken together, our data underline the importance of afadin and Cdh2 in the regulation of neocorticogenic mechanisms that, when perturbed, cause behavioural deficits, and might help to provide new insights into ASD pathogenesis.

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PS4-03

Transcriptomic correlation of the topographic afferent innervation distribution in the habenular complex.

Ms. Iris Juárez-Leal[1], Ms. Estefanía Carretero-Rodríguez[2], Ms. Francisca Almagro-García[1], Prof. Salvador Martínez[1], Dr. Diego Echevarría[1], Dr. Eduardo Puelles[1]

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The Limbic System is composed by circuits that regulate emotional sensations and self-protective behaviours (i.e. feeding, fighting or reproduction) and circuits that correlate expressive states and feelings of sociability and procreation. Among the several subcortical neuronal components of this system, the Habenula (Hb) seems to play a crucial centered role. The Hb is constituted by two main domains, the medial and the lateral Habenula (mHb, lHb). The afferences to the habenular complex, despite having different origins, are concentrated in a single tract, the stria medullaris (sm). This fascicle can be subdivided into two groups depending on their target (either mHb or lHb domains).

Recently, the subnuclear organization of both domains has been deeply analysed. The mHb subnuclei present a well stereotyped boundaries with differential gene expression profile while the lHb subnuclei are composed of many distinct cell types with a non-predicted molecular heterogeneity.

Our hypothesis is that the transcriptomic subdivision of Hb has a functional role in the limbic system circuits. Thus, we analysed the sm different innervation terminations by means of Hb transcriptomic subdivision. We used the Mouse Brain Connectivity section of the Allen Mouse Brain Atlas (www.allenbrainatlas.org) and selected eleven origin nuclei that project into the Hb complex. Our results suggest that septal nuclei would mainly innervate the ventral portion of the mHb. Meanwhile, pallidal nuclei would innervate the dorsal aspect on the mHb. Finally, the hypothalamic nuclei would innervate the lHb in a less compartmentalized manner. We therefore, may conclude that afferences to the Hb display a topographic-transcriptomic distribution. This distribution may underlay the still poorly understood internal circuitry in the Hb complex.

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PS4-04

Developmental origin of adult neurogenesis: Analysis of the postnatal hipocampal neurogenic niche in Sox5 conditional mutants

Cristina Medina Menéndez[1], Lingling Li[1], María Valdés[1], Rafael López-Sansegundo[1], Inés Colmena[1], Véronique Lefebvre[2], Aixa V. Morales[1]

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During embryonic and postnatal development of the dentate gyrus (DG), neural stem cells (NSCs) proliferate, migrate and generate mature granule neurons. In sharp contrast to other brain regions, in the DG a subpopulation of NSCs, are set aside in the subgranular zone (SGZ) and continues generating new granular neurons throughout adult life. One of the characteristics that distinguish adult NSCs most clearly from their embryonic counterparts is the acquisition of quiescence, by which adult NSCs remain for long periods out of the cell cycle. While most of NSCs will remain in a dormant state of deep quiescence throughout life, the transitions back and forward from an active /proliferative state to a temporal shallow quiescence or resting state, ensure the lifelong maintenance of the hippocampal stem cell population. However, it is unclear when and how adult NSCs acquire dormant or resting quiescence during development.

We have recently determined that SoxD transcription factors are required for the transition from quiescence to activation in NSCs and for the generation of new neurons in the adult SGZ. Now, we have determined that abolishing Sox5 expression in DG during development (using a Nestin-cre line; Sox5Nestin mice) provokes a drastic decrease in NSCs proliferation during the first postnatal weeks and a decrease in neurogenesis. Surprisingly, by P30, Sox5Nestin mice show an enhancement of RGLs proliferation, a reduction in RGL quiescence and an increase in neurogenesis. Moreover, we have established that at P30 the transitions between a primed /superficial quiescence and active/proliferative state are severely altered in NSCs from Sox5Nestin mice. Finally, by P150, the pool of NSCs and that of new neurons are reduced, indicating that in the absence of Sox5 the life-long maintenance of the adult neurogenic niche is compromised. Thus, our studies reveal a critical time window around P14-P30 when dormant and resting quiescence is established and when Sox5 plays a crucial role.

PS4-06

Effects of Lis1 gene loss in parvalbumin expressing cells on the mouse hippocampal cytoarchitectonics

Ms. Ana María Jiménez[1], Dr. Abraham Andreu-Cervera[1], Ms. Francisca Almagro-García[1], Dr. Eduardo Puelles[1], Dr. Diego Echevarría[1], Prof. Emilio Geijo-Barrientos[1], Prof. Salvador Martínez[1]
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Type I lissencephaly is a severe developmental brain disorder caused by mutations in the Lis1 gene. Despite the recent advances in understanding its functions, it is not fully understood the roles of Lis1 in specific neuronal populations during development and how these roles may modulate the maturation and function of the central nervous system (CNS).

Inhibitory GABAergic interneurons are important players in regulating the correct migration and activity of excitatory pyramidal neurons necessary for a proper functional maturation of the cortex. These interneurons express Lis1 and it is well known that a disruption of the balance and coordination between excitatory pyramidal neurons and inhibitory interneurons result in deep alterations of the brain functions such as epilepsy.

To address the unexplored role of Lis1 in GABAergic interneurons and its contribution to neurological disorders etiology and associated brain malfunctions, we generated a new mouse model specifically targeting the loss of Lis1 at the parvalbumin positive (PV+) GABAergic interneurons (Lis1cKO-PV+).

The hippocampus of postnatal (P15-P21) Lis1cKO-PV+ mice displayed a severe phenotype characterized by the presence of neuronal heterotopia affecting to the CA2/CA3 regions. In this hippocampal area the pyramidal cell layer was disorganized and there was an abnormal placing of pyramidal neurons from the stratum oriens to the stratum radiatum. These histological data highlighted, for the first time, that the specific role of Lis1 on the hippocampal GABAergic PV+ interneurons had a non-cell autonomous impact on the surrounding neural population of this cortical region.

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

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PS4-07

Cerebellar abnormalities in a conditional mouse mutant of the Lis1 gene

Dr. Abraham Andreu-Cervera[1], Ms. Ana María Jiménez[1], Ms. Mar Azorín[1], Ms. Francisca Almagro-García[1], Dr. Eduardo Puelles[1], Dr. Diego Echevarría[1], Prof. Emilio Geijo-Barrientos[1], Prof. Salvador Martínez[1]
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The cerebellum is related mainly to the coordination and regulation of locomotor activities such as control of fine movements, equilibrium, motor learning, and ocular movements. The formation of cerebellar neuronal circuits and the development of the physiological functions of the cerebellar cortex require a precise cortical sequence of neural differentiation and migration steps.
The Lis1 gene regulates the dynein dependent axonal transport, mediates neuronal migration in the developing brain, and supports synaptic integrity in the mature brain. In human, defects in LIS1 expression produce lissencephaly type I and is probably related to other neurological disorders such as schizophrenia. Lis1 is expressed throughout the entire lifespan of the central nervous system, but little is known about its potential role in the development and mature structure of the cerebellum, and particularly about the consequences of Lis1 dysfunction in specific neuronal types.
Parvalbumin(PV) is highly expressed in cerebellar Purkinje cell layer(PCL) during the formation and maturation of this cerebellar sheet. We have studied the cerebellar alterations caused by the selective inactivation of Lis1 in PV expressing neurons, creating a conditional Lis1 knockout mouse in PV+ neurons (Lis1cKO-PV+).
During prepuberal stages(P15-P21), Lis1cKO-PV+ mice presented a strong ataxic locomotor phenotype, reflecting possible dysfunctions in the cerebellum. At the cellular level, PCL displayed a clear impaired organization. Anatomically, Purkinje cells presented an abnormal soma with a rudimentary and atrophic dendritic arborization. Moreover, V-Glut1, a glutamatergic neuronal terminals marker, showed an abnormal organization of the excitatory basket nets generated by these terminals around the Purkinje soma. Altogether, these data suggest that Lis1 expression in Purkinje cells is not only required for their proper development and therefore the PCL organization but also for the normal synaptogenetic mechanisms leading to the organisation of the glutamatergic presynaptic terminals. These results also indicate the presence of non-cell autonomous effects of Lis1 dysfunction.
Work supported by MINECO/AEI/FEDER(SAF2017-83702-R), GVA(PROMETEO/2018/041), ISCIII("RD16/001/0010"), ERDF/ESF,"Investing in your future",WOP, and FTPGB(FTPGB18/SM) to S.Martinez. The Institute of Neurosciences is a "Centre of Excellence SeveroOchoa(SEV-2017-0723)".

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PS4-08

Cerebral cortex development is coordinated by mitochondrial reactive oxygen species

Ms. Regina Mengual[1,2], Dr. Cristina Rodríguez[1,2], Dr. Verónica Bobo-Jímenez[1,2], Dr. María Delgado-Esteban[1,2], Prof. Juan Pedro Bolaños[1,2,3], Dr. Angeles Almeida[1,2]

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The nervous system is particularly sensitive to reactive oxygen species (ROS) (1). Under physiological conditions, ROS regulate cell proliferation, neuronal differentiation, and synapse maintenance, indicating a key role of ROS in neuronal function and homeostasis. Moreover, mitochondrial ROS (mROS) generated by astrocytes regulate brain metabolism and behavior. Particularly, the reduction of astrocytic mROS in the adult alters neuronal structure and integrity leading to cognitive decline (2). However, the impact of mROS generation in the developing brain is unknown.

Here, we used mice genetically engineered to constitutively express a mitochondrial tagged enzyme catalase (mCAT) to downmodulate endogenous mitochondrial ROS generation (2).

We found higher levels of neuronal markers, TAU and MAP2, and increased neurite outgrowth in primary cortical neurons from mCAT, in comparison with wild-type (WT) neurons, at 3 days in culture. Then, mROS downregulation accelerated neuronal differentiation in vitro. Next, we evaluated whether the decreased mROS in the brain altered neurogenesis in vivo. Downregulation of mROS altered neurogenesis and layer organization in cerebral cortex from E15 mice. The proportion of cells expressing the progenitor cell marker NESTIN was lower, whereas that expressing neuronal markers TUJ1 and MAP2, was higher in the E15 mCAT cortices, compared to WT. Moreover, number of proliferating cells (BrdU-positive cells) in the ventricular/subventricular zones was lower, whereas immature neurons (TUJ-1 positive cells) were enriched in the interzone layer of E15 mCAT cortices, in comparison to WT. This was accompanied by an altered cortical radial distribution of MAP2 positive neurons in the cortex of E15 mCAT.

Our results suggest a key role of endogenous mROS levels in cell proliferation and neurogenesis onset, which would coordinate layer patterning in the cerebral cortex during brain development.

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PS4-09

The impact of NMDA receptor subunit GluN3A deletion on the brain activity of young and adult mice

Ms. Alicia Alonso-Andres[1], Dr. Oliver Crawley[1], Ms. Ana Isabel Navarro[1], Dr. John F. Wesseling[1], Dr. Isabel Pérez-Otaño[1], Dr. Ramon Reig[1]

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The maturation of functional sensory circuits with the capacity to process information is a highly orchestrated process that takes place during postnatal stages. It involves the interplay of progressive and regressive events that will stabilize some synapses and remove others. Problems during this critical period contribute to a wide spectrum of neurological disorders in later life. The pruning of axons and dendrites is controlled by multiple factors, one of them being the activity sensed and transmitted by N-methyl-D-Aspartate receptors (NMDARs). Here we focus on a new class of NMDARs that are characterized by the presence of GluN3A subunits and play an essential role in the activity-dependent refinement of synaptic connections. In mouse primary somatosensory cortex (S1) GluN3A expression peaks around postnatal days 6-9 and declines until reaching very low adult levels, with temporal differences between cortical layers (Murillo et al., Cereb Cortex 2020). Results from our collaborators show that GluN3A-containing NMDARs participate in axonal refinement in such a way that knocking out the gene encoding GluN3A (Grin3a) results in an aberrant pattern of callosal innervation of S1. Therefore, in this study, we investigated the impact of GluN3A deletion on the communication between hemispheres, and analyzed the spontaneous activity and sensory processing in S1 of juvenile (P20) and adult (P40) mice. To that end, we performed multi-site bilateral recordings of spontaneous activity in S1 of awake GluN3A knockout mice (Grin3a-/-). Preliminary results reveal changes in the power of several frequency bands in Grin3a-/- compared to wild-type mice at P20. We are currently characterizing the ipsilateral whisker responses in S1, which are mediated by callosal inputs. Understanding the dynamics of intra- and interhemispheric processing will shed light on the role of the GluN3A-containing NMDARs.

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PS4-10

In vitro study of neurodevelopment in Huntington's disease

Dr. Phil Sanders[1,2,3,4,5], Dr. Waseem Abbas[1,2], Dr. Anna Esteve-Codina[6,7], Dr. Gustavo Rodriguez-Esteban[1,2,6,7], Georgina Bombau[1,2,3,4,5], Mireia Galofré[1,2,3,4,5], Andrea Honrubia[1,2,3,4,5], Dr. Holger Heyn[6,7], Prof. Petia Radeva[8,9], Dr. Josep M. Canals[1,2,3,4,5]

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Huntington's disease (HD) is a neurodegenerative disorder that primarily affects the medium spiny neurons (MSNs) of the striatum. Recent evidence indicates that there is a neurodevelopmental component to HD where MSN specification, maturation and cellular homeostasis may be affected. However, the dysregulated cellular mechanisms underlying these impairments remain to be established. To enhance understanding of how neurodevelopment is affected in HD, further study of striatal development in a healthy context is also required as it is a brain region whose development is relatively understudied.

To investigate human striatal development in both a healthy and HD context, we differentiate control and HD human pluripotent stem cells in vitro towards an MSN fate. A range of analyses including bulk RNA-seq, single cell RNA-seq (scRNA-seq), and functional assays are performed during differentiation to evaluate the progression of striatal development and how it is altered in HD.

Bulk RNA-seq analysis indicates that alternative splicing is affected in HD cells. A set of neurodevelopment-related genes display differential expression of specific isoforms that is likely to impact on neuronal development and function.

scRNA-seq analysis has identified two main neuroblast populations. Using machine learning we have mapped the developmental trajectories that neural precursor cells follow to acquire these neuroblast identities. By plotting the expression of known striatal development genes onto these trajectories, we identify additional genes with a similar expression pattern that are also likely to have a role in striatal development.

Analysis of this diverse range of data sets is ongoing as they are integrated to develop a predictive model of striatal development. Using this approach, we anticipate that we will identify genes, signaling pathways and developmental modules whose modification will revert MSNs in HD to a healthy state.

PS4-11

Increased GABA levels in postnatal development alter cortical inter-hemispheric circuits

Ms. Lorena Bragg-Gonzalo[1], Dr. Marta Nieto[1]
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The corpus callosum (CC) is the largest fiber tract of the brain, connecting the two cerebral hemispheres and integrating sensory, motor, and higher-level cognitive information. The excitatory-inhibitory balance is crucial for sculpting cortical networks during the early postnatal period. Defective CC connectivity during this developmental period can correlate with defects in information processing in the adult, such as those observed in autism or schizophrenia. Here, we developed an experimental setup that alters excitatory-inhibitory balance in mice by injecting Diazepam –an agonist of the inhibitory neurotransmitter GABA– at specific postnatal windows. The number and location of callosal neurons were characterized via stereotaxic injections of the retrograde tracer cholera toxin B (CTB) in the CC of the primary somatosensory and visual areas (S1 and V1). We found that intraperitoneal injections of Diazepam result in a reprogramming of the interhemispheric adult circuit. In S1 there is a striking increase in layer 4 callosal neurons, while in V1 both layer 2/3 and 4 are increased. Interestingly, injections during the first postnatal week preferentially altered S1 over V1, while later treatments produce greater changes in V1 compared to S1. Furthermore, immunostaining of GABAergic markers to evaluate the status of the inhibitory circuit revealed a decrease in the total number of somatostatin interneurons and an increase in the parvalbumin population. Overall, our data show that disrupting the excitatory-inhibitory balance during development leads to alterations in both the inter-hemispheric and interneuron networks, perhaps in an attempt to maintain network homeostasis. We show that Diazepam-dependent plasticity is restricted temporally depending on the sensory area, possibly related to each area's critical period of plasticity. Further experiments using chemogenetics and electrophysiology will address whether the observed reprogramming is due to the activity of pyramidal neurons.

PS4-12

CB1 RECEPTORS DEFICIENCY IN OLIGODENDROCYTE PRECURSORS DISRUPTS POSTNATAL OLIGODENDROGENESIS AND CAUSES HYPOMYELINATION IN MICE

Aníbal Sánchez-de la Torre[1,2,3], Tania Aguado[1,2,3], Alba Huerga-Gómez[1,2,3], Juan Carlos Chara[4,5], Krisztina Monory[6], Carlos Matute[4,5], Beat Lutz[6], Susana Mato[4,5], Manuel Guzman[1,2,3], Ismael Galve-Roperh[1,2,3], Javier Palazuelos[1,2,3]

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Exogenous and endogenous cannabinoid molecules have been shown to modulate oligodendrogenesis and developmental CNS myelination. However, the cell-autonomous action of these compounds on oligodendrocyte precursor cells (OPC) in vivo has never been explored. Here, by using OPC-specific genetic mouse models we show that selective CB1 cannabinoid receptor depletion in OPC prevented cell differentiation and perturbed oligodendrogenesis and postnatal myelination. Moreover, early postnatal CB1 depletion in OPC caused hypomyelination and motor alterations at adult ages in mice. Conversely, CB1 receptor pharmacological activation promotes oligodendrocyte development and CNS myelination in wild type but not in OPC-CB1-null mice. Overall, this study addresses a cell-autonomous role for CB1 receptors in OPC modulating oligodendrogenesis that may help in understanding the complex network of signaling molecules that drives CNS myelination.

PS4-13

NMDA receptors containing GluN3A subunits influence myelination during development and after injury

Ms. Alice Staffa[1], Dr. Juan Carlos Chara Ventura[2], Dr. Carlos Matute[2], Dr. Isabel Perez-Otaño[1]
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NMDA receptors containing GluN3A subunits (GluN3A-NMDARs) are key modulators of the experience-dependent refinement and consolidation of neuronal circuits during critical periods of postnatal development (Nat Rev Neurosci, 2016). Together with their known effects on synapse selection, unbiased RNAseq analyses suggested that GluN3A-NMDARs modulate myelination. Specifically, we find that: 1) mRNAs encoding a wide range of myelin-related genes are upregulated in GluN3A knockout (KO) mice relative to wild-type; 2) enhanced MBP levels and myelinated axons are observed in somatosensory, motor or visual cortices during the second postnatal week (postnatal days P11-P18), but not at later stages when GluN3A levels are normally down-regulated; 3) the effect can be observed in adult mice upon demyelinating lesions of the CNS.

At the mechanistic level, the myelination phenotype was not due to enhanced numbers of oligodendrocyte precursor cells (OPCs), but to a faster or increased differentiation of existing OPCs. Because GluN3A is expressed both by neurons and oligodendrocytes and the cross-talk between them is essential for proper circuit function, we are now applying: i) mouse genetics to delete GluN3A from oligodendrocytes using Sox10-Cre mice; and ii) neuronal activity stimulation by DREADDs in total and Sox10-Cre KO mice to discriminate between oligodendrocyte and neuronal contributions to the observed phenotypes. Our working hypothesis is that GluN3A coordinates the maturation and consolidation of neural circuits by controlling the on-off switch of regulatory pathways that modulate the selection of synaptic connections and ensuing myelination of associated axons.

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PS4-14

COGNITIVE FUNCTIONS THAT RELY ON DORSAL HIPPOCAMPAL SYNAPTIC PLASTICITY PROCESSES INVOLVE A G-PROTEIN DEPENDENT MECHANISM THROUGH ADENOSINE A1 RECEPTOR-ACTIVATED GIRK CHANNELS

Dr. Souhail Djebari[1], Dr. Sara Temprano-Carazo[1], Dr. Irene Sánchez-Rodríguez[1], Mr. Guillermo Iborra-Lázaro[1], Dr. Agnès Gruart[2], Dr. José M. Delgado-García[2], Dr. Lydia Jiménez-Díaz[1], Dr. Juan D. Navarro-López[1]
[1]University of Castilla-La Mancha; NeuroPhysiology and Behavior Laboratory, Ciudad Real, Spain, [2]Pablo de Olavide University, Sevilla, Spain

A1 adenosine receptor-mediated GirK (G-protein-gated inwardly rectifying potassium) channels conductance is constitutively active in dorsal CA1 neurons contributing to the resting membrane potential. Its disruption has been linked to the etiology of many diseases that involve neural excitability alterations, such as Alzheimer's disease, suggesting a critical role of GirK channels for cognitive processes that depend on hippocampal neuronal activity.

Here, we aimed to explore the role of A1 adenosine receptor-mediated GirK basal activity in the regulation of synaptic plasticity processes supporting dorsal hippocampus-dependent cognitive capabilities.

To achieve this aim, we pharmacologically modulated basal GirK channel conductance in the dorsal hippocampus by using A1 adenosine receptor modulators or by direct selective manipulation of channel activity and we examined its involvement in controlling synaptic plasticity processes at different levels of complexity.

First, using mice dorsal hippocampal slice preparations, we examined pharmacological A1 receptor and GirK channel activity modulation effect on the induction and maintenance of long-term synaptic plasticity at CA3-CA1 synapse. Additionally, using an in vivo approach, we performed acute intracerebroventricular injections of GirK selective modulators to study their contribution to CA3-CA1 synaptic plasticity and subsequent learning and memory functions.

Our data indicates that a G-protein dependent mechanism through A1 adenosine receptor-activated GirK is required for long-term synaptic plasticity processes in dorsal hippocampus, as both A1 receptor and GirK channel activity modulation modified LTP/LTD induction threshold ex vivo and in vivo, even transforming HFS-induced LTP into LTD. Also, the disruption of such mechanism leads to hippocampal plasticity-dependent learning and memory deficits as shown during the behavioral tasks such as open field habituation.

Together, these results provide evidence that A1 adenosine receptor-mediated GirK basal activity governs hippocampal synaptic plasticity direction, which has a significant impact on hippocampal-dependent cognitive functions.

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PS4-15

Morphological Characterization of the Whale Retina

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The retina of the largest adult mammal in the world, the whale, was analysed morphologically by immunohistochemistry. The eye of these aquatic mammals have been poorly studied, thus, the aim of this study was to examine the different neurons and glial cells in the whale retina using a range of molecular markers.

The eyes of beached whales (n= 2, Balaenoptera physalus and Balaenoptera borealis) were obtained, and after dissection and fixation of the retinas, whole-mount preparations and cryostat sections were immunostained. The neurons and glial cells in these tissues were analysed using different antibodies to label RGCs, photoreceptors, bipolar cells, amacrine cells, microglia, astrocytes and Müller cells. Thioflavin S was also used to label misfolded proteins.

Most of the molecular markers used labelled their specific structures in the whale retinas as in terrestrial mammalian retinas. However, whale cones do not express cone markers (M/L and S opsin, and cone arrestin). It is important to highlight the large size of whale RGCs and there are a heterogeneity in NFs expression. It is also noteworthy that intrinsically photosensitive RGCs labelled with melanopsin form an extraordinary network in the whale retina, where these cells are more abundant in the centre, and different subtypes of melanopsin positive-cells were identified. Thioflavin S is weakly labelled of some RGCs in a punctuate pattern and it could easily represent an early sign of neurodegeneration. In addition, degenerative neuritic beading has been observed in RGCs when the retina was analysed after 48 hours postmortem.

In conclusion, there are some notable differences in the retina of the whales when compared with that of terrestrial mammals. Their rod-monochromatic vision due to an evolutionary loss of cone photoreception and the well-developed melanopsin-positive RGCs network could in part be responsible for their perception in the deep sea.

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PS4-16

Characterization of Primary and Immortalized Whale Müller Glial Cells

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Müller cells are the principal glia of the retina, expressing growth factors, neurotransmitter transporters and antioxidant agents with an important role in preventing excitotoxic damage to neurons. Although fish Müller cells can be transformed into neurons, this has never been described in mammals. In the present study, whale Müller cells were cultured and immortalized, with the aim of analysing the molecular characteristics as well as the division rate in vitro of primary and immortalized whale Müller cells.

The eye of Balaenoptera borealis was obtained, retina was isolated and Müller cells were cultured. Half of the cultures were immortalized with simian virus 40 T-antigen. Primary as well as immortalized Müller cultures were grown until primary cells reached senescence. Specific Müller molecules, dedifferentiated, neuronal precursors and neuronal markers were studied in both primary and immortalized cells. Ultrastructural morphology was also studied by scanning electron microscopy (SEM). In addition, the proliferation kinetics (time between divisions, percentage of dividing cells and division duration) was analyzed by time-lapse. Karyotype characterization was performed in immortalized whale Müller cells.

Whale Müller cells were immortalized after 10 passages and approximately 2 months of culturing. Müller markers were preserved, while expression of dedifferentiation markers was observed after the 5th passage. At high passages, neuronal precursor markers were weakly expressed. In addition, immortalized cells were stained extensively with neuronal markers. Immortalized Müller immunostaining and SEM revealed heterogeneous cell morphologies due to changes in the cytoskeleton. The proliferation kinetics demonstrated that primary whale Müller cells divides every 23 h, approximately, while after the immortalization process the time between divisions increased to 29 h.

In conclusion, we have generated a cell line from whale Müller cells that maintains primary Müller characteristics but presents a partially dedifferentiated state. In addition, we present a detailed analysis of the rate of cell division during the immortalization process.

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PS4-17

Impact of aging on the structure and NMDA receptor expression of somatostatin expressing hippocampal interneurons

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Aging is a natural process related to the gradual loss of physiological, behavioral, and social functions. Understanding the neurobiology underlying age-related impairment is essential given the growing elderly population. Among these mechanisms, changes in the structure of neurons and particularly in their dendritic spines are thought to be crucial players in age-related cognitive decline. One of the most studied brain structures affected by aging is the hippocampus, known to be involved in different essential cognitive processes. While the aging-associated quantitative changes in dendritic spines of hippocampal pyramidal cells have already been studied, the relationship between aging and the structural dynamics of hippocampal interneurons remains relatively unknown. Spines are not a frequent feature in cortical inhibitory neurons, but these postsynaptic structures are abundant in a subpopulation of somatostatin expressing interneurons, particularly in oriens-lacunosum moleculare (O-LM) cells in the hippocampal CA1. Previous studies from our laboratory have shown that the spines of these interneurons are highly plastic and influenced by NMDA receptor manipulation. Thus, in the present study, we have investigated the impact of aging on this interneuronal subpopulation. The analyses were performed in 3-, 9-, and 16-month-old GIN mice, a strain in which somatostatin positive interneurons express GFP. We studied the changes of dendritic spines, en passant boutons, and NMDA receptors (GluN1 and GluN2B) using confocal microscopy and image analysis. We observed a significant decrease of the dendritic spine density in 9-month-old when compared with the 3-month-old animals. We also observed a decrease in the expression of the GluN2B subunit, but not of that of GluN1, during aging. These results will constitute the basis for more advanced studies of the structure and connectivity of interneurons during aging and their contribution to cognitive decline.

PS4-18

Competition of transcriptional programs for transcriptional co-activators upon neuronal activation

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Activity-driven transcription is essential for the consolidation of memory processes and other long-lasting behavioral changes, contributing to the etiology of important neurological disorders such as epilepsy. CREB- and AP1-dependent gene expression have been identified as critical transcriptional factors for neuronal activity-driven transcription. Furthermore, histone acetylation has been correlated with neuronal transcription during memory acquisition and formation. Our laboratory has recently demonstrated the involvement of CBP and p300, two histone acetyltransferases and transcriptional co-activators that are known to interact with CREB and AP1, in the maintenance of neuronal identity. However, the functional cooperation between transcriptional factors and epigenetic complexes during neuronal activity is not yet defined. To investigate this cooperation, we integrated transcriptomic, epigenetic and chromatin structural data from the adult mouse hippocampus generated by our laboratory in the context of an experimental model of status epilepticus. Our multiomic analysis shows that neuronal activation causes a dramatic, but transient, genomic redistribution of CBP and p300, and CBP/p300-dependent H3K27 acetylation. Together our experiments and analyses unveil an intriguing competition between neuronal homeostasis and plasticity transcription, that can have important implications in neuropathology, and demonstrate a specific role for CBP/p300 in the transcriptional changes occurring during neuronal activation.

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PS4-19

Signaling mediated by the CREB-regulated transcription coactivator-1 (CRTC1) regulates NMDA-dependent synaptic plasticity

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Activity-dependent remodeling of synapses (i.e, synaptic plasticity) is considered the cellular basis of several brain physiological processes, including learning and memory. Synapse-to-nucleus signaling plays an important role in glutamatergic synaptic plasticity by linking the activation of N-methyl-D-aspartate receptors (NMDARs; GluN) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs; GluA) to gene transcription. The synaptonuclear factor CREB-regulated transcription coactivator-1 (CRTC1) connects glutamate receptor activation to CREB-dependent genetic programs at the nucleus, contributing to neuronal development, survival and plasticity. By contrast, CRTC1 deregulation is associated with dendritic pathology and cognitive dysfunction in neurodegenerative disorders. The CRTC1-dependent molecular mechanisms regulating NMDA-mediated synaptic plasticity in brain physiology and pathology remain poorly understood. In this study, we employed biochemical, cellular and electrophysiological techniques and gain and loss of function gene expression approaches to elucidate the role of CRTC1 in glutamate receptor modulation in the hippocampus. We found that CRTC1 overexpression or silencing have opposite effects on GluN1 expression, protein kinase C/A (PKC/PKA)-mediated phosphorylation and synaptic localization without affecting total and phosphorylated GluA levels. CRTC1 mediates NMDAR transmission and synaptic potentiation in the hippocampus by regulating (PKC)-induced phosphorylation and synaptic recruitment of GluN1. These results suggest that besides contributing to expression of neuroplasticity-related genes into the nucleus, CRTC1 may play a local role by regulating NMDAR localization at synapses.

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PS4-20

Aging entails motoneuron deafferentation and neuroinflammation in the mouse spinal cord

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Aging is accompanied by functional and structural alterations in the neuromuscular system. The causative factors of sarcopenia associated with aging are controversial and poorly understood, hampering the development of effective therapeutic interventions.

In the present study, we simultaneously analyzed changes in distinct components of the neuromuscular system of young, adult, middle-aged and old C57BL/6J mice, including: motoneurons (MNs), glia, and motor nerves.

We found that aging was not accompanied by a significant loss of spinal MNs, although a proportion of them in old mice exhibited an abnormally dark appearance. Morphological alterations in motor axons were already noticed in adulthood but substantially increased with age. We observed prominent microgliosis and astrogliosis around MNs, with significant increased density of pro-inflammatory M1 microglial and A1 astroglial phenotypes, and reduced proportion neuroprotective M2 microglia and A2 astroglia. Microglial cells exhibited an activated state in old mice, as we found a reduction in the length of branching and an increase in phagocytic markers inside these cells. Moreover, aged MNs were depleted of cholinergic and glutamatergic afferent terminals, the density of V0c interneurons was reduced and dorsal root ganglia cell populations were affected in terms of size and number, all of this suggestive of age-associated alterations in MN excitability and firing.

Overall, these results provide a global view of age-associated changes in the neuromuscular system of mice. Further work is necessary to examine the relevance of gliosis in MN deafferentation occurring with aging and the impact of both processes in motor-activity defects found in the elderly.

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PS4-21

The Y172 antibody against phospho-c-Jun (Ser63) selectively detects an unidentified protein present in motoneurons and Schwann cells, two sidekicks of the neuromuscular system

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To drive motor behavior, the excitation state of motoneurons (MNs) is controlled by different inputs. The C-bouton is one of the main excitatory synapses on MNs. Alterations in C-boutons appear to play an important role in MN pathology, particularly in atrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA). During an immunocytochemical study on the role of c-Jun in MNs with a monoclonal (clone Y172) antibody against phospho-c-Jun (serine [Ser]63), we observed an unexpected labeling closely associated to C-boutons.

We further analyzed the Y172 immunostaining in the spinal cord MNs of CD1 mice and mouse models of SMA (Smn2B/-) and ALS (SOD1G93A). Additionally, we extended the study to the sciatic nerve.

In adult spinal cord, MNs displayed strong Y172 immunostaining in cytoplasmic structures associated with C-boutons, but not with other synapse types on MN somata and proximal dendrites. By ultrastructural analysis, cytoplasmic Y172 immunostaining was selectively located at the subsurface cistern of C-boutons. The analysis of Y172 immunoreactivity in injured MNs after peripheral nerve transection, and in SOD1G93A and Smn2B/- mice, revealed a significant depletion of cytoplasmic immunostaining. RNA interference experiments to knockdown c-Jun in vitro resulted in no reduction in the density of cytoplasmic Y172-positive profiles. Studies in the sciatic nerve revealed that the Y172-immunoreactivity was also present in the cytoplasm of Schwann cells ensheathing MN axons.

Overall, we show a novel unidentified molecular component of the C-bouton organization, which expression is lost in damaged MNs even before the occurrence of cholinergic deafferentation. Moreover, the presence of Y172 in Schwann cells suggests that this protein may play an important role in MN maintenance. Our results lay the foundation for further studies aimed at identifying the Y172-related protein and determining its role in the context of the development, maintenance, plasticity and pathology the neuromuscular system.

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PS4-22

Effects of balanced vs. deficient omega-3 fatty acid diets on adult hippocampal neurogenesis and glia

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Maternal dietary intake of the polyunsaturated fatty acids omega-3 (Ω3) and omega-6 (Ω6) impacts brain function, specifically hippocampal development. Current trends in dietary habits have dangerously reduced the intake of Ω3. The hippocampus is involved in memory and it is one of the most plastic regions of the brain. Indeed, newborn neurons continuously integrate into the hippocampal dentate gyrus (DG). We postulate that deficient-Ω3 diets affect the cellular composition of the DG after the postnatal periods, as its development continues through life. Thus, we fed young male and female mice (1.5 months old) with either Ω3 balanced or deficient isocaloric diets for ten weeks. As Ω3 and Ω6 are precursors of inflammatory regulators, we injected mice six weeks before sacrifice with bacterial lipopolysaccharide (LPS), a well-known inducer of inflammation and long-term negative modulator of neurogenesis. Our results revealed an effect of diet on adult neurogenesis (number of stem cells and new neurons) and microglia. Surprisingly, new neurons significantly decreased in female mice fed with the Ω3-deficient diet but not in male mice. However, LPS did not affect neurogenesis or microglia but induced a long-term reduction in astrocytes regardless of the diet. Further analysis is required to adequately evaluate the modulatory action of Ω3 dietary balance on the long-term effects of LPS mediated inflammation. In conclusion, dietary Ω3 deficiency alters the cellular composition of the young DG by affecting adult neurogenesis and microglia. Notably, adult neurogenesis is especially affected in female mice. Our study points to the relevance of balancing Ω3 dietary intake to preserve brain health.

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PS4-23

Afferent synaptic terminals on spinal cord motor neurons are acutely disrupted after peripheral nerve transection: involvement of necroptotic pathway and microglial piecemeal phagocytosis

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The disconnection of motor neurons (MN) from their skeletal muscle targets, as occurs after a peripheral nerve section, leads to a rapid recruitment of reactive microglia in the affected regions of the spinal cord. We reported that the degeneration of synaptic inputs on axotomized MNs occurs closely associated with activated recruited microglia. Synaptic terminals undergo disrupted and fragmented leading to extracellular vesicles before they are "ingested" by microglia. These observations are in contrast with the classical concept of synaptic stripping in which afferent terminals are detached from the surface of axotomyzed MNs by microglia without degeneration signs.

To explore the interactions between recruited microglia and presynaptic terminals on lesioned MN somata we have performed electron and confocal microscope analysis of axotomized MNs between 1 - 15 days after sciatic nerve transection in mice.

Between 1 and 3 days post-injury, microglial cells surrounding the injured MNs were highly phagocytic showing an increased expression of the lysosomal marker CD68. After ultrastructural examination we did not observe bulk engulfment of synaptic boutons by microglia. Instead, microglia internalized small membranous-vesicular fragments originated from the disruption of synaptic terminals. Abundant extracellular vesicles in the perineuronal space after axotomy were seen together with the expression of the necroptosis effector protein p-MLKL, and later, with the appearance of exosomal markers. Moreover, activated microglia and synaptic boutons displayed C1q immunoreactivity, suggesting a contribution of the complement to the microglial-mediated synaptic elimination.

Overall, our data reveals new mechanisms by which afferent synapses are removed from acutely injured MNs. Microglia is actively involved in eliminating fragments of damaged presynaptic terminals. Furthermore, our data is relevant in the context of neuroinflammation and MN disease as well as for understanding the functional recovery after peripheral nerve injury.

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PS4-24

Relationship of FAIM-L and Ovarian Tumor (OTU) Deubiquitinases in synaptic remodelation

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A correct regulation of the nuclear factor-kappa B (NF-κB) transcription factor is critical for synaptic processes, neurotransmission and neuroprotection. Recently, deubiquitinase A20, a well known negative regulator of NF-κB in immune system, has been involved in synaptic functions. In primary hippocampal neurons, A20 negatively regulates dendritic spine density in an NF-κB activation-dependent manner; however the molecular mechanism requires further clarification.

A20 belongs to a family of deubiquitinating cysteine proteases named ovarian tumor (OTU) family which contains other A20-like proteins such as OTUD7A (Cezanne2) and OTUD7B (Cezanne). Primary cortical neurons from Cezanne2-null mice show decreased total spine density and activity compared to wild-type neurons, showing an opposite function of what described for A20. However, little is known about the molecular pathways and partners associated to Cezanne2 in neurons.

Our group has previously shown that the neuronal form of Fas Apoptotic Inhibitory Molecule (FAIM-L) participates in non-apoptotic functions of caspases such as axonal degeneration and synaptic plasticity. By stabilizing XIAP, FAIM-L regulates AMPAR internalization after NMDA-induced LTD and regulates axonal pruning after NGF deprivation.

Since FAIM-L, A20 and Cezanne2 participate in synaptic remodelation and plasticity, we first studied whether they are able to interact. We observed that A20 interacts specifically with neuronal isoform, FAIM-L, and not with ubiquitously isoform, FAIM-S, under overexpression conditions. In addition, preliminary results reveal that FAIM-L could regulate the stability of A20 either directly or indirectly. Furthermore, we are studying whether the other A20-like proteins, in particular Cezanne2 could also specifically interact with the neuronal form of FAIM.

Given all this, we hypothesize that FAIM-L interaction with A20 or Cezanne2 could modulate their role in synapses. Therefore, examining the implications of these interactions in physiological and pathological conditions, such as neuroinflammation and neurodegeneration, will provide crucial information for better understanding the molecular mechanisms of dementia.

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PS4-25

Potential neuroprotective role of lysophosphatidic acid receptor 1 overexpression by hippocampal neurons in a model of temporal lobe epilepsy

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Lysophosphatidic acid receptor 1 (LPA1) is a G-protein coupled receptor involved in cell proliferation, survival differentiation and other biological processes. In the adult rodent brain, LPA1 specifically labels hippocampal neural stem cells (NSCs) which generate newborn neurons throughout postnatal and adult life in most mammals.

Interestingly, LPA1 also labels Reactive-NSCs (React-NSCs). The reactive glia-like counterparts of NSCs induced by seizures and that abandon neurogenesis to transform into reactive astrocytes and contribute to gliosis.

Further, using a transgenic mouse line in which the enhanced green fluorescent protein is expresses under the regulatory elements of LPA1 (LPA1-GFP) we have stablished that React-NSCs lose LPA1 expression several weeks after seizures, as they differentiate into reactive astrocytes. In parallel, neurons of the granule cell layer start to express LPA1 gradually in the epileptic brain and maintain its expression in the long term.

Using confocal microscopy imaging of control and epileptic LPA1-GFP mice we are currently evaluating whether LPA1 expression promotes the survival of neurons in granule cell layer. In addition, we are using hippocampal NSC-derived neuronal cultures to activate or inhibit LPA1 inducing cell death to better asses it potential role in neuroprotection.

PS4-26

The primary cilium as an organelle for astrocyte-neuron communication.

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Primary cilia are microtubule-based organelles present in the plasma membrane of most cell types, including mature astrocytes and neurons. The primary cilium has emerged as a major signalling hub in the cell; however, little is known about the role of this organelle in the mature brain. Data from our lab show that neuronal cilia is required for soluble amyloid beta oligomer signalling and modulation of autophagy, and that these events are modulated by physiological aging.

Here, we hypothesize that similarly to neuronal cilia, astrocytic primary cilium senses and transduces extracellular signals and that it reacts to changes in neuronal cilium. We also hypothesize that aging might alter cilia-related events in old astrocytes. To test our hypothesis, we have studied how the loss of primary cilia in neurons induces changes in astrocytes, astrocytic primary cilia, and cilia-related autophagy. For that, we have studied by IHC astrocyte reactivity and morphology in young and old IFT88::SLICK-H mice, a mouse model where cilia is lost in mature Thy1+ neurons. In these mice, we have also characterized astrocyte cilia presence and their morphology, as well as changes in the major autophagy markers. Moreover, we have deleted primary cilia in human astrocytes as well as in human neurons and established an in vitro model of astrocyte-neuron co-culture, with the aim to study the dynamics of astrocyte and neuronal cilia changes between these two cell types. Overall, we aim to understand the role of mature astrocytic primary cilia in the brain, as well as its interplay with neurons and their possible changes during aging.

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PS4-27

Transgenic expression of mutant versions of CSPalpha/DNAJC5 causes lipofuscinosis in mice

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Mutations in the DNAJC5 gene, that encodes the synaptic vesicle protein Cysteine String Protein alpha (CSPα) cause adult-onset autosomal dominant neuronal ceroid lipofuscinosis (CLN4) (Noskova et al, 2011), a devastating neurodegenerative disease affecting young adults. In humans, two-point mutations (Leu115Arg and Leu166Del) independently cause CLN4 by unknown mechanisms. In order to investigate the disease mechanisms in vivo, and since the disorder is autosomal-dominant, we have used a pronuclear injection approach to generate mouse lines overexpressing CSPα variants under control of the neuronal specific Thy1 promoter. We have generated three independent lines that express GFP-fusion proteins of three different versions of CSPα/DNAJC5: WT, Leu115Arg and Leu166Del. The mice are viable and do not show any obvious morbidity or mortality increase. Transgenes are well expressed all over the hippocampus, however, the WT version in particular is strongly expressed at mossy fibers in contrast to the mutant versions. The existence of autofluorescent punctate structures that are labelled with antibodies against ATP synthase subunit C in Leu115Arg, but also in Leu166Del transgenics, suggest an increase of lipofuscinosis in the mutants. Immunohistochemical analysis with markers of granulovacuolar degeneration bodies, excluded the involvement of this neurodegenerative lysosomal pathology. Next, we used transmission electron microscopy (TEM) to find at pyramidal neurons of the CA3 region structures similar to granular osmiophilic deposits (GRODs) previously described in NCL4 patients. The GROD-like structures were present only in the mutants but not in the negative controls or the transgenics overexpressing the WT version. Furthermore, we could not detect GROD-like structures or other signs of increased lipofuscinosis in conventional or conditional knock-out mice lacking CSPα/DNAJC5. We concluded that CSPα/DNAJC5 mutant versions might cause lipofuscinosis by preferentially hijacking key proteins that could include, but not only, endogenous CSPα/DNAJC5. We expect our novel mouse models will help to identify those proteins.

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PS4-28

A mouse genetic strategy to investigate the role of CSP alpha/DNAJC5 in glutamatergic synaptic function and maintenance

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Cysteine String Protein (CSPα/DNAJC5) is a synaptic co-chaperone that prevents activity-dependent degeneration of synapses. CSPα/DNAJC5 knock-out mice suffer from a neurological phenotype and early postnatal lethality soon after the first month of age. CSPα/DNAJC5 is critical to maintain the levels of the SNARE protein SNAP25, especially in highly active synapses. Indeed, the decrease in SNAP25 levels is thought to be a key event leading to presynaptic neurodegeneration. We are interested in studying the synaptic effects of removing CSPα/DNAJC5 from adult glutamatergic neurons that operate at a low activity regime. Based on a mouse line bearing a Dnajc5 floxed allele (Nieto Gonzalez et al., Proc. Natl. Acad Sci. USA, 2019) we have used the CamKIIαCreERT2 mice (Erdmann et al. BMC Neurosci. 2007) to conditionally target Dnajc5 in adult hippocampal glutamatergic neurons (CaMKCreERT2:Ai27D:Dnajc5flox mice). This line also expresses channelrhodopsin2 fused to the fluorescent reporter td-tomato (Ai27D) in targeted neurons. CSPα/DNAJC5 conditional knock-out mice survive and do not develop an evident neurological phenotype. We have analyzed synaptic transmission in two hippocampal synapses: (1) synapses formed by mossy fibers at CA3 pyramidal neurons (mf-CA3 synapse) and (2) synapses formed by Schaffer collaterals at CA1 pyramidal neurons (sc-CA1 synapse). Interestingly, those synapses show different phenotypes in the absence of CSPα/DNAJC5. We are investigating the molecular mechanisms of such a phenotype to understand why those apparently similar synapses have different requirement of CSPα/DNAJC5 and how those differences might be related to SNAP25.

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PS4-29

Acute genetic elimination of a synaptic co-chaperone in adulthood to study protein stability in neurodegeneration

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Neurons and synapses operate during decades to sustain brain function throughout life. Synaptic proteins last only for several days or weeks. The mechanisms by which synaptic proteins are maintained are not well understood yet. We are interested in the mechanisms of action of a trimeric chaperone complex (CSPα/DNAJC5-SGTA-HSC70) involved in that process and to identify key client proteins. Conventional knockout mice lacking CSPα/DNAJC5 develop presynaptic degeneration and die soon after birth, making extremely difficult studies in adulthood. We have bred mice bearing the Dnajc5 floxed allele (Nieto Gonzalez et al. Proc. Natl. Acad. Sci. USA. 2019) against UBC-Cre-ERT2 mice (Ruzankina et al. Cell Stem Cell. 2007) to target Dnajc5 ubiquitously in a time-controlled manner. CSPα/DNAJC5 is almost undetected in hippocampal cultures of UBC-Cre-ERT2:Dnajc5flox/flox mice after 13 days in tamoxifen. Next, to investigate the function of CSPα/DNAJC5 in adulthood we fed 2 months old UBC-Cre-ERT2:Dnajc5flox/flox mice with tamoxifen during 15 days. Two weeks after ending tamoxifen administration, mice exhibited weight loss and a neurological phenotype characterized by loss of spontaneous activity, strength and motor coordination. This lead, two weeks later, to early death. We focused on hippocampus to detect, as expected, a general decay in the levels of CSPα/DNAJC5 transcript (RNAscope) and protein (western-blot). However, using immunofluorescence, we detected that the level of decay of CSPα/DNAJC5 was not the same in different hippocampal synaptic layers. This suggests that CSPα/DNAJC5 lifetime is not only determined by its amino acid sequence but also by environmental influences such as the specific neuronal type and/or the network activity. This novel mouse model will be used to investigate changes in protein stability related to neurodegeneration.

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PS4-30

Nucleus Accumbens Astrocytes Control The Cognitive Impairment Derived From Chronic Exposure To THC

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The nucleus Accumbens (NAc) is a key region of the reward system implicated in motivation, drug addiction and numerous neurological and psychiatric disorders. A remarkable feature of this nucleus is the integration of motor and limbic information from glutamatergic inputs. Due to the relevance of this communication, it is crucial the maintenance of glutamate homeostasis, which is altered by addictive drugs. Moreover, there is solid evidence that the modulation of synaptic transmission is mediated by activation of cannabinoid receptors type I (CB1Rs) in astrocytes, suggesting that astrocytic CB1Rs are involved in glutamate homeostasis and modulate long-distance communication between neuronal populations. However, the functional role of astrocytes in alterations derived from chronic drug exposure is not fully understood.

In this study, we have analyzed the role astrocytes play in alterations produced by tetrahydrocannabinol (THC), the psychoactive constituent of marijuana. For that purpose, we have removed specifically the protein p38αMAPK, which mediates exocytic release of glutamate, from NAc astrocytes (Navarrete et al., 2019). First, using fiber photometry in vivo we analyzed glutamate dynamics and astrocytic activity in NAc after 1mg/kg THC chronic administration in wildtype (wt) and p38αMAPK-/- (Astrop38α) mice. Then, we performed behavioral tests to assess whether THC had reinforcing properties or affected learning and memory. Furthermore, using a chemogenetic approach (DREADDs) we activated NAc astrocytes to analyze the behavioral implications. And finally, we performed electrophysiology experiments to analyze synaptic plasticity. We observed: 1)THC administration increases astrocytic calcium activity in wt and Astrop38α; 2)THC administration induces glutamate release in NAc in wt, which is not present in Astrop38α; 3)Astrocyte signaling mediated by CB1R induces NMDAR-LTD at NAc; 4)NAc astrocytes are involved in learning; and 5)Removal of p38αMAPK in NAc astrocytes restores the cognitive impairment derived from THC treatment.
Altogether, our results reveal astrocytes as critical elements for the maintenance of glutamate signaling, with a significant role in drug-consumption related alterations.

PS4-31

A critical period for the itch spinal cord neural circuit?

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Itch is a widespread symptom associated with a diverse array of diseases. Despite its prevalence in the world population, our understanding of the development, maturation and mechanisms associated with itch neural circuits is lacking behind that of other somatosensory modalities. We have previously characterized the importance of spinal Ptf1a-derived inhibitory neurons in controlling the entry of innocuous mechanosensory information into the spinal cord dorsal horns. Loss of Ptf1a-derived adult neurons leads to the development of an intense chronic itch phenotype and increased hairy skin sensitivity. Here, we study the consequences of ablating Ptf1a-derived neurons both in early embryonic development, well before somatosensory input becomes active, and in newborns, when somatosensory circuits are being refined with the arrival of extrinsic stimuli. Our results show that postnatal loss of Ptf1a-derived neurons cannot be compensated, even as early as postnatal day 0, resulting in the development of chronic itch. However, elimination of these neurons during embryonic development leads to apparently normal itch sensation. The potential mechanisms explaining these observations point to the possible existence of a critical period for the establishment of functional itch circuits in the spinal cord. Moreover, these results suggest that loss of specific populations of inhibitory neurons in the dorsal horns activates endogenous compensatory mechanisms that yields a functionally normal mature spinal itch circuit.

PS4-32

AN ANALISYS OF TIMING CORRELATION REVEALS THAT MOTOR CORTEX NEURONS ARE RELATED, BUT NOT THE ORIGIN, OF CLASSICALLY CONDITIONING EYELID AND VIBRISSAE RESPONSES IN MICE

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Classical eyeblink conditioning is one of the experimental models more widely used for the study of the neuronal mechanisms underlying the acquisition of new motor and cognitive skills in behaving animals. Currently, certain studies are pointing out the motor cortex as the putative structure responsible of this type of learning, although other studies give this main role to the cerebellum. Other brain areas might be involved too. In order to determine the specific contribution of the motor cortex to the generation of learned movements, we studied the temporal correlation between unitary activities of identified eyelid and vibrissae motor cortex neurons, and the electromyographic activity of the orbicularis oculi and vibrissae muscles and magnetically recorded eyelid movements, during classical conditioning of eyelid and vibrissae responses, using both delay and trace conditioning paradigms, in behaving mice. Mice were prepared for classical eyeblink and vibrissae conditioning and for recording of the unitary activity of motor cortex neurons. Chronic electrodes for stimulation and recording were implanted in the eyelid and vibrissae muscles, and a craniotomy was carried out in the cerebellar skull. Eyelid movements were recorded with the help of a magnet fixed to it. Neurons were identified by their antidromic activation from the ipsilateral red nucleus or the contralateral facial nucleus. We also studied the involvement of motor cortex neurons in reflexively evoked eyelid responses and the kinematics and oscillatory properties of eyelid movements evoked by motor cortex micro-stimulations. Results show the involvement of the motor cortex in the performance of conditioned responses elicited during the classical conditioning task. However, a timing correlation analysis showed that both electromyographic activities (from orbicularis oculi and vibrissae muscles) preceded the firing of motor cortex neurons, which must therefore be related more with the reinforcement and/or proper performance of the conditioned responses than with their acquisition and storage.

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PS4-33

LARYNGEAL EFFECTS OF STIMULATION OF THE CUNEIFORM NUCLEUS IN SPONTANEOUSLY BREATHING ANAESTHETIZED RATS

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Background: The cuneiform nucleus (CnF) is a mesencephalic area that has been involved in sympathetic activity due its connectivity with several nuclei involved in cardiorespiratory control, e.g. dorsolateral periaqueductal gray matter (dlPAG), the parabrachial/Kölliker-Fuse complex (PBc/KF), the solitary tract nucleus (NTS) and the rostral ventrolateral medulla (RVLM). In previous studies we have demonstrated a functional interaction between hypothalamic and mesencephalic structures (DMH-PeF, dlPAG) with several pontine regions (PBc, A5) (Díaz-Casares et al., 2009, López-González et al., 2020). We have also shown that rostral and ventral pontine structures are involved in the changes of laryngeal caliber (Lara et al., 2002). The aim of this study was to characterise the relationship between mesencephalic-pontine neuronal circuits to understand their role in laryngeal control and its effect on vocalization.

Methods: Experimental studies were carried out with non-inbred male rats (n=7), [SPF, Sprague-Dawley (300-350 g)]. Animals were anesthetized with sodium pentobarbitone (60 mg/kg i.p., initial dose, supplemented 2 mg/ kg, i.v., as necessary). A double tracheal cannulation (upwards for the “glottis isolated in situ” technique, and downwards in the direction of the carina) was done. Subglottic pressure was recorded with a precision differential pressure transducer (ADInstrument model FE141, ± 0,03 psi) by passing a stream of humidified medical air upwards through the larynx at a constant rate of 30-70 ml/min with a thermal mass digital air flow meter controller (Bronkhorst Hi-Tec F-201CV-AGD-22-V). Electrical stimulation of the CnF using concentric bipolar electrodes (1 ms pulses, 20-40 µA, 100 Hz for 5 s) was performed. Respiratory flow, pleural pressure, blood pressure, heart rate and ECG activity were also recorded.

Results: CnF stimulation evoked a decrease of laryngeal resistance (subglottal pressure) ($p<0,01$) accompanied with an inspiratory facilitatory response consisted of an increase in respiratory rate ($p<0,01$), together with a pressor ($p<0,001$) and a tachycardic response ($p<0,01$).

Conclusions: The results of our study contribute with new data on the role of the CnF in the mechanisms controlling subglottic pressure and laryngeal activity.

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PS4-34

Noradrenaline innervation and Alpha adrenoceptors in the human and macaque higher-order thalamic nuclei.

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Noradrenaline (NA) modulates processes like sensorimotor gating and prepulse inhibition through higher order (HO) thalamic nuclei. Besides, the macaque HO nuclei are within the most densely innervated by NA and within those displaying the highest Alpha adrenoceptor concentrations. The purpose of this study is to compare the patterns of NA innervation and adrenoceptors in the macaque and human HO thalamic nuclei.

Human brain sections containing the thalamus were immunostained against the NA transporter to reveal the NA axons. Quantitative autoradiography was performed to reveal the adrenoceptors: the ligands [3H]-Prazosin (Alpha-1 receptors), [3H]-RX-821002 (whole Alpha-2 adrenoceptor population), and [3H]-UK-14,304 (high-affinity state Alpha-2 adrenoceptor) were used. The distributions of axons and receptors were compared to similar data from macaques, previously published.

The human mediodorsal nucleus (MD) showed moderate NA innervation, with the highest densities in the medial and ventral regions of the nucleus. Within the human pulvinar complex, the nucleus with the highest NA innervation was the oral pulvinar (Pul O); the medial pulvinar (Pul M) displayed moderate densities of NA axons, and the lateral and inferior pulvinar (Pul L, Pul I) presented low NA axon densities. The highest densities of Alpha-1 receptors were present in the dorsal and medial regions of MD, and in the medial regions of Pul M. The highest Alpha-2 receptor concentrations were present in Pul I. Pul O showed high Alpha-2 receptor revealed by [3H]-RX-821002 but rather low revealed by [3H]-UK-14,304 pointing to a low proportion of high-affinity Aplha-2 receptors in this nucleus.

The distributions of NA axons and Alpha adrenoceptors in the human HO nuclei are highly comparable to those in macaques. The main differences were in the Alpha-1 receptor concentrations, which were higher in macaques than in humans, and in the high-affinity Alpha-2 receptor concentrations in the PulO, which were also higher in macaques.

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PS4-35

Surprisingly dense projections from the ventral nucleus of the trapezoid body to the dorsal cochlear nucleus

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Animals integrate auditory and somatosensory stimuli because the perception of sounds depends not only on their position relative to the sound source, but also on the posture of the head and ears. This integration first occurs in the dorsal cochlear nucleus (DCoN). Key to the integration of different sensory modalities is the laminar structure of the DCoN, very similar to that of the cerebellar cortex. In the cerebellum, afferent information reaches mainly the deep layers and is subsequently transmitted to the superficial layers. However, the DCoN receives a presumably auditory afferent that, unlike what happens in the cerebellum, does not reach the deep layers: the projection from the ventral nucleus of the trapezoid body (VNTB).

Our goal was to carry out the first detailed morphological investigation of the projection from the VNTB to the DCoN of the rat. Using albino rats, we have performed two types of experiments. First, to analyze the distribution and morphology of the axons that innervate the DCoN, we injected the bidirectional tracer biotinylated dextran amine (BDA) into VNTB. Second, to characterize the neurons that give rise to this projection, we injected BDA into DCoN.

The VNTB-to-DCoN projection is very predominantly contralateral. VNTB axons form an amazingly dense terminal plexus restricted to the molecular layer and very rich in synaptic boutons. In this plexus, bands of higher density perpendicular to the pial surface alternate with bands of lower density. This projection is tonotopic.

VNTB neurons that innervate the DCoN possess medium-size multipolar cell bodies, occupy the central dorsoventral third of the nucleus and are distributed along the entire rostrocaudal length of the VNTB. They seem to belong to a hitherto unidentified neuron type.

These features suggest that the projection from the VNTB exerts an unknown, strong influence on the function of the DCoN.

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PS4-36

The power spectrum determines subthalamic beta bursts dynamics in Parkinson's disease

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Excessive beta oscillations (13-35 Hz) in the basal ganglia are considered a hallmark of Parkinson's disease (PD). The intermittent dynamic of pathological beta oscillations has been recently characterized in terms of beta bursts, expanding the unitary perspective of beta power in the frequency domain to a dualistic view of burst amplitude and duration in the time domain. However, the possibility that at rest beta burst amplitude and duration may simply reflect the stochastic fluctuation of a noisy beta oscillator, defined by the power spectrum, has not been fully tested. To formally address this issue, here we recorded local field potentials (LFPs) from the subthalamic nucleus (STN) of PD patients at rest OFF and ON medication. We modeled these LFPs as noisy oscillatory processes with two signal modeling methodologies based on the power spectrum, using autoregressive methods and the autocorrelation function. We found that the dynamics of beta bursts – i.e. their average amplitude and duration – did not differ between recorded and simulated beta oscillations. Furthermore, beta burst amplitude correlated with the power of the beta peak in the power spectrum, whereas beta burst duration correlated with the sharpness of the beta peak. We thus clarified that beta burst dynamics in the time domain have a direct correspondence in the frequency domain. Overall, our results suggest that the shape of the power spectrum largely determines the dynamics of beta bursts.

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PS4-37

SECRETAGOGIN EXPRESSION IN THE MOUSE BRAIN

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Calcium-binding proteins such as calbindin, calretinin or parvalbumin are essential for the correct functioning of the brain. Their distribution has been widely studied in the central nervous system, mainly for neuroanatomical purposes since they provide a “Golgi-like” staining with noteworthy details of neurites. Secretagogin is another calcium-binding protein that also provides a high-quality immunostaining of specific neuronal populations, but whose distribution throughout the brain is poorly known.

Here, we analysed the expression of secretagogin in the brain of adult mice by immunohistochemistry, identifying positive cell populations in different areas and nuclei according to Paxinos mouse brain atlas. Combined immunofluorescence was used for studying colocalization between secretagogin and other common calcium-binding proteins.

We observed many secretagogin-positive cells throughout the brain. The staining was remarkable in some areas of the olfactory bulb, basal ganglia, thalamus and hypothalamus. Surprisingly, no labelling was detected in cerebellum, where other calcium-binding proteins are widely distributed. Secretagogin-positive cell populations were very heterogeneous, concerning both size and distribution: in some nuclei positive cells occupied all the analysed area, but in others few disperse positive cells were observed. Interestingly, in some cases such distribution did not fit with the nuclei traditionally described, suggesting either neurochemical subdivisions for partial-labelled regions or shared functions for adjacent nuclei. Regarding colocalization, results were also very variable. Depending on the region, secretagogin colocalized with either calbindin, calretinin or parvalbumin, but in other areas, even with high neuronal density, no colabelling was identified and they were independent populations.

We conclude that secretagogin is present in many different neuron populations in the mouse brain. The function of these cells seems to be heterogeneous, and this protein is expressed either independently or in combination with other calcium-binding proteins. Secretagogin can be a useful neuronal marker in different brain areas for specific populations and its knowledge advances the complex regulatory mechanisms of calcium levels in the central nervous system.

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PS4-38

Identification of a fast hippocampal recognition system in humans using intracerebral evoked potentials

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The role of the hippocampal formation in memory recognition has been well studied in animals, with different pathways and structures associated to specific memory processes. However, due to the limited accessible information, the hippocampus is commonly analyzed as a unique responsive area in humans. Combining intracerebral electroencephalogram recordings in epileptic patients and blind source separation (BSS) methods, we identified several components emerging from the hippocampus, likely reflecting the activity of different substructures as CA1 or the dentate gyrus. In a memory task involving the recognition of old and new images, we found one hippocampal component with fast responses to the stimuli that could not be directly identified from raw recordings. This component was locally generated in the hippocampus and was different from the responses in other structures, including the entorhinal cortex. These results suggest that the hippocampus may have a fast memory recognition system that can be retrieved thanks to the use of BSS methods. This challenges previous studies pointing the entorhinal cortex as the first area involved in memory recognition, with similar delays to the novel hippocampal early response. We hypothesize that both regions are elements of the same recognition system and they would be virtually coactivated via the hippocampal-entorhinal loop, with time differences in the order of the synaptic delays between both structures.

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PS4-39

Chronic sensory deprivation alters cortical rhythms in the somatosensory cortex

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The somatosensory cortex is arranged in six layers characterized by different cellular populations and input/output connections. The laminar organization represent a key evolutionary feature that serve to transfer the spontaneous cortical activity vertically across layers from the same column and horizontally among different cortical areas. In this context, a spinal cord injury (SCI) produces a massive sensory deprivation of the somatosensory cortex that strongly affects the cortical activity in the long-term. However, whether spontaneous neuronal activity is equally affected across deprived cortical layers in time is less understood. Therefore, the main aim of this work is to identify physiological features of spontaneous neuronal activity localized in each cortical layer at different time points from acute to chronic stage of sensory deprivation (SCI). Experiments were performed in adult rats under control conditions and after SCI or sham lesion. To measure neuronal activity, we used electrophysiological recordings of local field potentials simultaneously obtained from all cortical layers by using a vertical array of 32 electrodes (50□m spaced). Data were obtained weekly after SCI to elucidate the temporal windows of cortical physiological changes. The spontaneous activity from each cortical layer were analysed by using a Fast Fourier Transform analysis to identify the power of frequency bands of interest: slow-wave (<1Hz), Delta (1-4Hz), Beta (12-25Hz) and Gamma (25-80Hz). Results show that physiological changes take place only in the SCI group during the 3rd and 4th weeks after SCI, while control group remain unchanged. Specifically, Delta activity was reduced in layers IV and V, while Beta and Gamma activity were increased in the infragranular layers V and VI. We conclude that a chronic sensory deprivation after SCI affects the cortical rhythms differently across layers and in a time-dependent manner. Changes in spontaneous activity could indicate alterations of neuronal network excitability, which could be part of the cortical reorganization phenomenon.

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PS4-40

Investigating the role of auditory cortex on decisions about sound lateralization

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Decisions are an essential part of life and almost all decisions involve some comparison between different options. Previous work from our group relates the mechanism for Weber's Law - accuracy of the discrimination between the intensity of two sensory stimuli depends only on their ratio - with a new mathematical regularity, the Time Intensity Equivalence in Discrimination (TIED) - changes in the absolute intensity of two stimuli being discriminated under a fixed intensity-ratio are completely equivalent to a change in the effective unit of time with which the discrimination duration is measured.
The TIED is incredibly restrictive and has allowed us to list a set of three computations required for the Weber's Law to be present: sensory relay, evidence accumulation and representation of the decision bound. We aim to identify the different brain regions responsible for these computations through testing of different candidate areas. We have predicted how perturbations to each of these computations would affect the behaviour through changes in accuracy and reaction time.
The focus of this project is on testing the involvement of the ACx as the sensory relay. Lesion studies based on the injection of an excitotoxic agent which led to a permanent lesion of ACx show how behavioural outputs do not seem to be affected by the ablation of ACx.
Permanent lesions allow for compensatory mechanisms to arise and do not allow a trial by trial manipulation of the decision, so we also show the results of optogenetic silencing of the ACx. We show that by using the stGtACR2 opsin we manage to achieve effective and robust silencing of the ACx while shining blue light onto the cortex during acute recordings. After this we developed a novel way to chronically implant LEDs in the skull of the animal in order to allow for optogenetic silencing of the whole ACx in behaving, freely moving rats. We also present preliminary data on how this perturbations affect the animals' decisions.

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PS4-41

Interference-based forgetting in a goal-directed spatial navigation task for rodents.

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To avoid catastrophic accumulation of information during learning the brain needs to forget to retain only what is subjectivity relevant to each individual. Interference-based forgetting occurs when new information acquired before or after a learning event attenuates memory strength. In our daily life we are continuously exposed to new associations, each with its own value and volatility, which limits the interpretation of results obtained in lab conditions using only few associations. For this reason, we developed a novel task that allows us to observe the effect of memory interference in more ethological conditions.

We utilized our high-throughput behavioral task where animals learn the location of the reward among 8 possible positions, that randomly changes across days. We test the memory recall of the location of the reward position 2 hrs after the training session and we observe how memories from previous sessions (i.e. days) interfere with this recently learned memory. To manipulate the interference between previously learned memories, we infused human N-Methyl-D-aspartic (NMDA) receptor and Leucine-rich glioma-inactivated 1 (LGI1) antibodies into animals' brain ventricles to mimic a partially anterograde amnesic state.

We confirmed that continuous learning of new associations decreases the strength of recent memories due to the interference with previous ones. We showed for the first time the effect of interference from all previous memories up to 3 days in the past. We also found that antibodies mediated amnesia is capable of reducing interference significantly ($p<0.01$) enhancing recent memories at the cost of considerably reducing (~40%) the strength of old ones. Our findings support the theory of retroactive interference as the mechanism to eliminate memories from associations with high volatility.

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PS4-42

Inhibition in a midbrain circuit controlling instinctive escape decisions

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To avoid predation, animals must choose from an array of defensive actions that are instinctive, yet adaptable to the environment. In mice, excitatory (VGluT2+) neurons in the dorsal periaqueductal gray (dPAG) compute the decision to escape from imminent threats by integrating synaptic input from the medial superior colliculus. Here, we show that inhibitory (VGAT+) dPAG neurons are an integral part of the escape initiation circuit, imposing a local inhibitory tone that determines the threshold for escape initiation.

We first characterised the intrinsic firing properties of dPAG neurons using loose-seal cell-attached recordings in acute midbrain slices of transgenic mice. We found that, even in the absence of synaptic inputs, VGAT+ neurons in the PAG fire action potentials spontaneously, whereas VGluT2+ neurons do not. Next, we combined whole-cell patch-clamp recordings with optogenetic and chemogenetic manipulations and found that VGAT+ neurons provide synaptic input onto neighbouring excitatory cells and exert local phasic inhibition on the dPAG network. Optogenetic inactivation of VGAT+ dPAG neurons in freely behaving mice increased the probability of initiating escape from innately aversive stimuli. Conversely, optogenetic activation of the same neurons during threat presentation inhibited escape initiation. To further understand the biophysical basis of local inhibition in the dPAG and its modulation, we performed single-cell RNA-sequencing on VGAT+ and VGluT2+ neurons individually isolated from acute midbrain slices. Differential expression analysis of these data identified candidate ion channel subunit and neuromodulator genes for setting and regulating key biophysical properties of PAG neurons.

This work shows that both the activity of excitatory dPAG neurons and the initiation of instinctive escape are controlled by a local GABAergic network, and provides a framework for studying how molecularly defined biophysical properties might underpin behavioural control by the PAG.

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PS4-43

Functional analysis of cholinergic neuromodulation of chandelier cells from single-cell to circuit

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Synaptic inhibition is responsible for orchestrating spontaneous and evoked activity in the neocortex. Chandelier cells (ChCs) are a subclass of GABAergic cortical interneurons that innervates the axon initial segment (AIS) of pyramidal neurons, controlling the cell firing output. Mostly localized at the boundary of layers 1 and 2 (L1-L2) in prefrontal cortex, they present an asymmetric distribution of dendrites, which are mostly oriented towards L1, which suggests that ChCs may receive input from other cortical areas and deep nuclei, such as basal forebrain, which projects the strongest cholinergic innervation to L1, implying a plausible role for ChCs as circuit switches. Our interest lies in studying the role of ChCs in the control of cortical network activity, with a special focus in the presumable cholinergic modulation of these cells. To identify the population of cortical ChCs, we used a mouse model expressing td-Tomato under control of precise Cre- and Flp- dependent promoters (Tasic et al., Nature 2018). Using immunohistochemical and electrophysiological techniques, we have described the existence of cholinergic neuromodulation through specific nicotinic receptors and the intrinsic electrophysiological properties of ChCs. To clarify the role of ChCs in the regulation of the prefrontal cortical circuitry, we performed in vivo 2-photon imaging experiments in awake animals using GECIs, showing that ChCs are active during arousal, and we used DREADDs to modulate their activity to uncover its inhibitory role in the control of the excitatory network. Our results demonstrate that prefrontal ChCs are a subpopulation of fast-spiking parvalbumin interneurons modulated by cholinergic inputs activated during arousal states in awake mice, with a prominent role in the control of the pyramidal neurons.

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PS4-44

Perceptual decisions results from the accumulation of unpredicted sensory evidence

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Accumulation of evidence (AE) and predictive coding (PC), two major frameworks for understanding perception, offer contrasting views on how incoming stimuli are integrated with beliefs about the current state of the environment. According to AE, sensory evidence is added to the current belief, allowing reliable temporal evidence integration in face of ambiguous stimuli. By contrast, PC suggests that predictions formulated from current beliefs are subtracted from novel sensory information, allowing rapid responses to changes in unambiguous environments. Here, we show that this apparent discrepancy can be reconciled within a bayesian framework that we call Accumulation of Unpredicted Evidence (AUE). In AUE, current belief is updated with the prediction error conveyed by each stimulus (unpredicted evidence) and not the raw stimulus evidence. AUE (but not AE) is the normative approach to perceptual decision-making when sequential dependencies exist between sensory information. We tested the AUE model in an auditory accumulation reaction-time task where we introduced sequential correlations between pairs of successive tones within a stimulus sequence. The AE model predicts that first and second tones in a pair (unpredictable and predictable tones, UT and PT) should have equal impact on perception. By contrast, in AUE, PTs impact on current belief is smaller, because part of PT evidence can be predicted from the previous tone. In agreement to AUE, UTs preceding subject choice had a larger impact on choices than PTs, as the decision threshold was more frequently reached after UT rather than PT presentation. Moreover, a central late positivity EEG signal, previously associated with the accumulation of evidence, showed a much stronger response to the UT than to PT evidence. This signal contrasted with a negativity EEG signal similar to the Mismatch Negativity, which scaled with the degree of sensory surprise associated with each tone. Overall, behavior and neuroimaging results confirm that perception relies on the accumulation of unpredicted evidence, combining the predictive component of PC with the integration properties of AE.

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PS4-45

PSICOICTUS: EVALUATION AND PROGNOSIS OF AFFECTIVE AND COGNITIVE DISORDERS AFTER MINOR STROKE

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The neurovascular unit (NVU) represents the structural and functional multicellular relationship between the brain and blood vessels. The NVU is vital for autoregulation of cerebral homeostasis and control of cerebral blood flow (CBF). Minor stroke (MS), a type of ischemic stroke, is defined as an episode of focal neurological symptomatology lasting more than 24 hours, and mild functional outcomes. Despite the neurological outcomes, a wide range of affective and/or cognitive disorders often occurs after MS. How MS would interrogate the NVU, as a disbalance, and how the simultaneous presence of both (MS and NVU) can affect the clinical outcome and determine long-term poor outcomes and dementia is still unknown. For that, evaluating the NVU in patients is essential to understand the pathophysiology of MS and define the clinical and cellular components. Psicoictus project aims to characterize the affective and cognitive profiles in MS patients by a neuropsychological battery, neuroimaging studies and serum biomarkers by metabolomics and lipidomics approach. Psicoictus is an observational, longitudinal and prospective study that includes patients with MS's diagnosis from January 2018 to March 2020. Patients are evaluated by a screening battery (MoCA, MADRS and AES-C) within five days from stroke minor diagnose. Subsequently, patients with affective and/or cognitive impairments in the screening battery are followed up at 15 days, 6 months and 1-year post-stroke. 178 patients were recruited and 118 patients were included: 31 (26%) had depression, 25 (21%) apathy and 28 (24%) cognitive impairment on the first screening. Patients with cognitive impairment were further evaluated by a complete neuropsychological battery, being executive functions and attention the most affected domains. The untargeted metabolomics and lipidomic defined a set of molecules on plasma samples obtained at 3-5 days post-stroke. The current study would validate a new diagnostic and prognostic strategy for MS patients and it brings evidence that a light disbalance of the NVU would have a potential long-term clinical outcome, being essential for interpretation of its physiopathology.

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PS4-46

Non-conventional GluN3A expression gates memory formation by limiting synaptic mTOR signaling in juvenile and adult mice

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GluN3A-containining NMDA receptors are key regulators of postnatal neuronal development. Thought to be downregulated after postnatal stages, remnants of GluN3A expression have been recently identified in specific areas of the adult brain (Murillo et al., Cereb Cortex, 2021), though the role is still unknown. Transgenic mouse studies show that synapses that express GluN3A are resistant to the induction of long-lasting functional and structural plasticity; and memories fade more quickly in mutant mice with prolonged GluN3A expression. In line with this work, humans with low levels of GRIN3A (human gene encoding GluN3A) perform better in cognitive tasks. Here we investigated the impact of GluN3A expression in cognitive functions and explored the underlying mechanisms. We found that developmental or genetic loss of GluN3A enables synaptic mTORC1-dependent translation and facilitates memory consolidation in spatial and associative tasks. Notably, unlike the memory enhancement seen after global manipulations of translation, GluN3A deletion does not compromise memory flexibility or extinction. The memory enhancement is evident since early postnatal ages and can also be achieved by adult deletion of GluN3A in excitatory neurons. These findings identify GluN3A as regulator of synaptic translational control during memory encoding, and offer a potentially selective target for cognitive modulation.

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PS4-47

The Hot Brain Hypothesis and a new type of interaction. A research on stress

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Introduction: The impact of emotions in education is a common fact not always transformed in a pedagogical principle and less in a research topic for validating a pedagogical method. The method y propose is based on the fluid (empathic, sincere and positive) interaction in a democratic encounter group. To explain how it works I constructed the Hot Brain Hypothesis that brings the perspective of an emotionally fueled cognitive process and states that emotions are fundamental for cognition, my self-cognition coefficient changing with the emotional involvement. The fluidity equation (N=103) and the empathy coefficient across different groups prove that fluidity is strongly connected with the emotional involvement in group interaction, that is, intensity of emotion is what counts.
Materials and methods: The experimental design consisted in a social stress test followed by an encounter group interaction, comparing salivary cortisol levels after each one of them (N=12). The psychological analysis was done using five types of questionnaires: depression, anxiety, empathy, stress and my fluidity questionnaire (Cronbach α=0.8).
Results: Cortisol levels decreased after the group interaction, proving that fluidity is reducing participant's stress. The fluidity equation that describes the connection between my fluidity and the fluidity of the participants and of the group captured the impact of stress.
Conclusion: As the HPA axis in the stress test experiment is reflecting the limbic system reaction, especially amygdala's reaction, but by prefrontal cortex modulation through empathy, this allows the Hot Brain Hypothesis to predict the impact of emotions on cognitive processes in line with the regression analysis results and to explain the impact of an empathic interaction in the reduction of stress, decreasing cortisol levels, proving that the fluid interaction is therapeutic.

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PS4-48

Stress research and implications for the neuropsychiatric classification of emotion related brain functioning

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Introduction: My research of the effect of stress on adolescent brain functioning has validated the positive therapeutic impact of the fluid teaching interaction, based on a dimension of personality called fluidity (empathy, sincerity and positive interaction). Therefore, I propose a new hypothesis about a quadruple brain functioning classification (supercold, cold, hot and superhot brain) that has implications from the neuropsychiatric perspective of establishing a diagnostic and of an efficient therapeutic intervention.
Materials and methods: I administered empathy, depression, anxiety questionnaires and my fluidity questionnaire (Cronbach α=0.8). Comparing the psychological database (N=103) and the stress test database (N=12), I constructed four neuropsychological types of brain functioning by emotion-cognition criteria. The cognitive coefficient used was my own self-cognition coefficient.
Results: The supercold brain that approximates a psychopathic personality has fifteen times more cognitive bias than the normal hot brain group. The superhot brain that approximates an anxious and depressive personality has a lower cognitive bias. I also validated the superhot brain type with two subjects that have a clinical diagnostic.
Conclusion: The four brain types capture the variation of cognitive processes by the variation of empathy and anxiety/depression in strong correlation with DSM taxonomy, proving to be a useful instrument to describe brain emotion-cognition activity. I present some criteria and elements of each category and at the same time I argue that the proposed classification of brain functioning from the emotion-cognition interaction perspective surpasses the linear and clear-cut partition and offers arguments for the four types of brain functioning as a psychiatric classification on a continuum but also, mutatis mutandis, as four modes of everyday brain functioning in an active-adaptive strategy to a changing social context.

PS4-49

DREAM protein inhibition as potential treatment against metabolic syndrome and its associated neurologic signs

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High fat diet (HFD) chronic intake induces metabolic syndrome in mice, characterized by a body weight increase and insulin resistance (IR). Obesity is a risk factor in the development of neurodegenerative diseases, neuropsychiatric disorders and is associated with cognitive decline. DREAM/kchip3/calsenilin (DREAM) is a multifunctional protein that belong to neuronal Ca2+ sensors family. Previous studies have demonstrated the relevance of DREAM in nociception and in learning and memory processes. In the present study we characterize the consequences of DREAM, genetic or pharmacologic, inhibition in the metabolic and behavioural alterations caused by HFD intake in mice. Our results showed that chronic pharmacological and genetic DREAM inhibition block the metabolic syndrome development, and both of its neurologic comorbidity symptoms: the anxiety-related behaviour, and the cognition deficiency. Also, pharmacologic DREAM inhibition when metabolic syndrome is established did not affect metabolic parameter but improved metabolic syndrome-related neurologic alterations. Therefore, in this study we demonstrate: DREAM inhibition may be a potential treatment to restore neurological symptoms related with metabolic syndrome; and to block metabolic syndrome induced by HFD intake.

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PS4-50

Is your gaze your aim? Eye position in reward gambling and the role of orbitofrontal cortex in encoding the value of visually cued offers.

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A wealth of studies has revealed how cells in frontal brain areas are involved in cognitive control functions. Of crucial interest is the understanding of how the activity of neural cells relates to the processing of external stimuli features bound in abstract entities of behavioral relevance, thus playing a functional role in cognitive control tasks requiring working memory and decision making. For decision making tasks with sequential reward offers presentation, neurons in the orbitofrontal cortex (OFC) have been associated with the coding and maintenance of the estimated value of a firstly presented offer so that it can be later compared with the estimated value of a later presented one. Importantly, it is yet to be assessed what is the role of perceptual features of visually presented offers such as the order of presentation and their spatial location. Our research aims to investigate the role of task variables in eye movement behavior and the role of neural activity in OFC during the execution of a two-alternative gambling task with sequential visual offer presentation. Interestingly, we report that eye movements consistently fell within the visual screen side with best offer expected value, thus showing how eye position can be used as a marker of readout of the actual best guess. In addition, despite the subjects were left with blank screen and free to direct gaze at their will, we found that they most frequently reached the side of best offer at each time during task execution. We find evidence for this behavior soon after the first offer was presented and, very consistently, soon after the second offer presentation. Lastly, we investigated the role of cells in OFC, revealing how a significant portion of cells shows linear tuning in their firing rate with respect to offer features. In particular, we report spatial selectivity to the side of presentation, to the order of presentation of offers with different values, and to the value of rewards achieved in previous trials.

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PS4-51

Behavioral mechanisms underlying visually-guided control of steering

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Goal-directed behaviour involves navigating in an environment in order to fulfill a particular objective. In order to attain their goal, animals, and agents in general, need to keep track of many variables critical in the system, such as location and heading direction for spatial navigation. In particular, processing of optic flow for visually guided navigation is crucial for the estimation of heading direction, taking part in a perception-action loop where heading informs the control of the observer's movement, which in turn modifies the pattern of optic flow at the next instant of time. Whereas human behavioral studies have extensively examined how optic flow contributes to goal-directed navigation, virtually nothing is known about the neural processing of optic flow that guides navigation. In addition, previous studies that have measured neural responses to optic flow during behavior have used forced-choice psychophysical tasks that are open-loop. In order to address these gaps, we introduce a simple navigation task in which a monkey needs to steer a joystick to align themselves to a cued target, which is not visible during steering, in a virtual environment that only provides noisy optic flow feedback that is a direct consequence of the monkey's actions. We develop a minimal and interpretable stochastic optimal control model that captures important features in the data such as urgency to reach the goal and reactive, closed-loop control in the presence of external perturbations. We also show, consistent with previous findings, that multiplicative control noise plays an important role in the reproduction of the monkey's control behavior. Identifying the dynamical variables that govern steering through our model is an important first step to study in future work how control-related signals might be used and represented in the brain and how the neural processing of optic flow guides realistic, closed-loop, navigation.

PS4-52

A novel visuospatial working memory task in mice

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Working memory (WM), defined as the ability to maintain and process information in our brain for a short time, is a cornerstone of cognition. It is involved in many cognitive processes and is impaired in multiple mental disorders. Despite decades of study, the neural circuit mechanisms underlying this key brain function remain debated.

Aiming to better understand limits of WM, we have developed a visuospatial WM task in mice inspired by classical work carried out in primates. Subjects are trained to look and memorize the location of a visual stimulus displayed in a touchscreen. After a variable delay period, mice had to report the remembered position by touching the screen.

In this task, animals made two types of errors: non-memory dependent, present in visually-guided trials; and memory dependent, they increase gradually with delay length. Part of these memory dependent errors are caused by idiosyncratic biases that increase as a function of delay. We hypothesize that idiosyncratic biases are induced by discrete attractor dynamics pulling memories towards a few stable representations in mnemonic space.

We also analyzed the repeating bias, defined as the excess of probability of making a particular response rt=X after the previous choice rt-1 is also X. We fit a linear mixed model to the repeating bias data and we observed a significant increase with delay length ($p=0.004$) suggesting that this type of choice bias could be a bias in WM caused by previous stored locations.

This novel task presents an opportunity to investigate visuospatial WM in mice, an animal model suited for circuit level electrophysiology, genetic and pharmacologic manipulations and models of mental disorders associated with a WM malfunction such as schizophrenia.

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PS4-53

Mechanisms of post-stroke cognitive impairment: hippocampal involvement

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Stroke produces a progressive impairment of hippocampus-dependent memory in ~40% of mice exposed to the ischemic insult and stimulates neurogenesis in adult rodent dentate gyrus. Recent studies suggest that newborn neurons after stroke show an aberrant morphology and may therefore incorrectly integrate into the pre-existing hippocampal circuits, leading to the cognitive impairment observed (Cuartero et al., 2019). The mechanisms by which these alterations occur are unknown. Based on these findings, our main objective is to explore the possible alterations of the neurogenic niche components, which could be related to a deterioration of hippocampal-dependent memory after stroke.

To perform this study, stroke was induced by occlusion of the middle cerebral artery (MCAO) in 2-month old C57Bl/6 male mice. Different hippocampal metabolites and neurotransmitters were analysed by magnetic resonance spectroscopy and episodic memory was evaluated using the contextual fear conditioning test. The number of microglia, astrocytes, parvalbumin+ and somatostatin+ interneurons was analysed by immunofluorescence and confocal microscopy.

Our results show that the levels of some metabolites and neurotransmitters changed after ischemia, including Glutamate + Glutamine, N-acetylaspartylglutamic acid + N-acetylaspartate, glycerophosphocoline (GPC), inositol and GABA. GPC, which is usually associated with cellular turnover, was increased after stroke; this increase might be reflecting the changes in neurons at the population level including the cycle of proliferation and maturation of the newborn neurons. Also, ischemia induced gliosis and astrogliosis with astrocyte activation and an increase in inositol, which is considered a glial marker. Interestingly, higher hippocampal GABA levels at 14 days after ischemia correlated with worse memory at 35 days ($n=15$; $P<0.05$); in agreement, there was an increase in the number of hippocampal immunoreactive somatostatin+ interneurons.

In conclusion, our results suggest that experimental stroke by MCAO in mice induces hippocampal alterations which may account for the neurogenic alterations associated with the cognitive deficit observed.

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PS4-54

A role of 14-3-3ζ in transformation of labile short-term object recognition memory into stable long-term memory

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The consolidation of new memories into long lasting memories is multistage process characterized by distinct temporal dynamics. However, our understanding on the initial stage of transformation of labile memory of recent experience into stable memory remains elusive. Here, with the use of rats and mice overexpressing a memory enhancer called regulator of G protein signaling 14 of 414 amino acids (RGS14(414)) as a tool, we will show that the expression of RGS14(414) in male rats perirhinal cortex (PRh), which is a brain area crucial for object recognition memory (ORM), is able to enhance ORM to the extent that it causes the conversion of labile short-term ORM (ST-ORM) expected to last for 40 min into stable long-term ORM (LT-ORM) traceable after a delay of 24 h and that the temporal window of 40 to 60 min after object exposure not only is key for this transformation but also is the time frame when a surge in 14-3-3ζ protein is observed. A knockdown of 14-3-3ζ gene abrogates both the increase in 14-3-3ζ protein and the formation of LT-ORM. Furthermore, this 14-3-3ζ upregulation increases BDNF levels in the time frame of 60 min and 24 h and 14-3-3ζ knockdown decreases the BDNF levels, and a deletion of BDNF gene produces loss in mice ability to form LT-ORM. Thus, within 60 min of object exposure, 14-3-3ζ facilitates the conversion of labile ORM into stable ORM, whereas beyond the 60 min, it mediates the consolidation of the stable memory into long lasting ORM by regulating BDNF signaling.

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PS4-55

Role of the galanin N- terminal fragment (1-15) in the mesolimbic dopaminergic system

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Role of the galanin N- terminal fragment (1-15) in the mesolimbic dopaminergic system

We have recently discovered that Galanin(1-15) [GAL(1-15)] induced depression-like behaviour in the Forced Swimming Test and Tail Suspension Test. Since anhedonia is a core feature of depression, we have analyzed in rats GAL(1-15) actions in anhedonic-like behaviour tests: Saccharin self-administration test, Novelty Suppressed Feeding (NSF) and Female urine sniffing test (FUST). To investigate the areas involved in GAL(1-15) effects, we have analyzed transcriptional changes in the VTA and NAc. We have also studied the impact of GAL(1-15) on other reinforcers, specifically on the effect of alcohol.

In the saccharin Self-administration, a dose-response curve of GAL(1-15) 1nmol, 3nmol was performed. In NSF and FUST, we have analyzed GAL(1-15) 3 nmol effects in the latency of the first feeding episode and the female urine sniffing duration. The VTA and NAc were dissected from the NSF and FUST experiments, and RT-qPCR measured the mRNA expression of C-Fos, Dat and, Vmat2.
In the two-bottle choice test, groups of rats received i.c.v. GAL (1-15) 1, 3nmol or vehicle 2hours before the measures.
One-way ANOVA followed by Fisher´s least significant difference test was used.

GAL (1-15) 3nmol significantly increased the latency of feeding ($p<0.001$) in the NSF and significantly decreased sniffing duration ($p<0.001$) in the FUST. In the VTA, GAL(1-15) 3nmol produced a significant decrease in the mRNA levels of Dat and Vmat2 ($p<0.05$). In NAc, GAL (1-15) induced a significant reduction in the expression of C-Fos mRNA.
GAL (1–15) 3nmol significantly decreased the ethanol intake ($p<0.05$) and preference ($p<0.05$).

These results suggest the participation of the mesolimbic dopaminergic system in action mediated by GAL(1-15) on anhedonia and ethanol consumption, paving the way for its use in other drugs of abuse.
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PS4-56

EPILEPTIC SEIZURE PREDICTION WITH A LSTM NETWORK

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Over the years, epilepsy research has focused on discovering its aetiology, designing appropriate treatments and improving patients' quality of life. One of the key elements for the latter two goals is to know when an epileptic seizure episode is going to occur, since knowing the window in which an attack will occur well in advance makes it easier to control it with the necessary therapeutic measures and reduces the uncertainty and stress suffered by the patient.
Predicting an epileptic seizure requires an artificial intelligence algorithm that integrates a series of data in real time.
Predicting an epileptic seizure requires an artificial intelligence algorithm that integrates a series of real-time data. This data can be from motion, heart rate or even optical sensors, but the best predictor to date is the patient's own brain signals.
In this study, an artificial neural network has been developed with the aim of predicting epileptic seizures in a dataset obtained from multi-electrode arrays. For this purpose, a data processing software has been programmed to obtain the most relevant spectral and morphological characteristics of the signals, namely: spectrogram, Welch power estimate, spectral entropy, zero-crossing rate, total signal area, mean, variance, skewness and kurtosis. This neural network has been trained on graphics processing units to speed up computation times and facilitate the parallelisation of the process.
The resulting neural network is able to predict with attacks in time windows of 15 minutes with an accuracy of 87.38%. Based on this network, future work will adapt the system to the EEG data and try to optimise the architecture to improve the results.

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PS4-57

Bump attractor dynamics underlying stimulus integration in perceptual estimation tasks

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Perceptual decision and continuous stimulus estimation tasks involve making judgments based on accumulated sensory evidence. Network models of evidence integration usually rely on competition between neural populations each encoding a discrete categorical choice. By design, these models do not maintain information of the integrated stimulus (e.g. the average stimulus direction in degrees) that is necessary for a continuous perceptual judgement. Here, we show that the continuous ring attractor network can integrate a stimulus feature such as orientation and track the stimulus average in the phase of its activity bump. We reduced the network dynamics of the ring model to a two-dimensional equation for the amplitude and the phase of the bump. Interestingly, these reduced equations are nearly identical to an optimal integration process for computing the running average of the stimulus orientation. They differ only in the intrinsic dynamics of the amplitude, which affects the temporal weighting of the sensory evidence. Whether the network shows early (primacy), uniform or late (recency) weighting depends on the relative strength of sensory stimuli compared to the amplitude of the bump and on the initial state of the network. The specific relation between the internal network dynamics and the sensory inputs can be modulated by changing a single parameter of the model, the global excitatory drive. We show that this can account for the heterogeneity of temporal weighting profiles observed in humans integrating a stream of oriented stimulus frames [1,2]. Our findings point to continuous attractor dynamics as a plausible mechanism underlying stimulus integration in perceptual estimation tasks.

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PS4-58

The inverse problem in intracerebral field potentials: a reappraisal of volume-conducted and local field potentials.

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Finding the deep sources that compose an EEG at the skull is termed the inverse problem, and cannot be solved without spatial information of the sources. However, the problem affects even further to intracranial recordings, which is usually neglected, but recent technical and theoretical developments have begun to address it adequately. The mixing of potentials in the volume causes the original temporal motifs to distort each other and vary at different sites. Thus the time-frequency parameters of brain waves (amplitude, phase, duration) may become stripped of physiological meaning. Here we explore how the FPs of one source modify the waveform parameters of others. Experimental data shows a conspicuous presence and far reach of FPs generated by primary structures as the cortex and hippocampus, which not only contaminate each other, but impose their temporal traits on large portions of the brain. Both contain several sources whose activation is state, region, and time-dependent. Feed forward simulations show that the reach of FPs is determined by the source's geometry. We noticed that discriminating potentials by distance to the source (volume-conducted vs local field potentials) is inadequate, particularly for large sources. For example, it is often forgotten that LFPs themselves are formed by mixing multiple nearby sources that blur each other's time course in the FP mixture, or that large sources can be near and far from an electrode. Altogether, the risks of assuming a "locality" and/or a single source origin for intracranial recordings are exposed, and we propose a broader view that prioritizes the geometry and the position of the sources over the distance to the electrodes. Obtaining the spatial demarcation of the active sources should be a primary objective together with their full disentangling to guide the correct treatment toward physiologically meaningful time courses of the activities in the neural networks.

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PS4-59

STRIATUM-ENRICHED TRANSCRIPTION FACTOR FOXP2 AMELIORATES EARLY PSYCHIATRIC-LIKE DISTURBANCES AND MOLECULAR ALTERATIONS IN HUNTINGTON´S DISEASE

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Patients with Huntington's disease (HD) may have difficulty controlling impulses and emotions, resulting in outbursts, yelling, or aggression. Mild to severe depression have been also widely reported. All these symptoms together are the ones of the primary complaints of HD. These disturbances have an early onset and could be associated to a very early dysfunction of the striatal circuitry. To understand how these psychiatric alterations take place, its underlying molecular mechanisms must be delineated.

Previous studies showed that the striatal-enriched gene Foxp2 is among the earliest genes dysregulated in the striatum of mouse models of HD. Foxp2 is a crucial gene for the formation and maturation of the cortico-striatal pathway. Coinciding with the HD pre-symptomatic psychiatric symptoms, it has been described in genomic wide association studies (GWAS) that Foxp2 is a major risk factor to develop depressive symptoms, irritability and sleep disturbances among others.

We performed a battery of behavioral tests in the juvenile R6/1 mouse model of HD to evaluate early psychiatric-like disturbances as impulsivity, aggressive behavior or hyperactivity.

We show that the detected dysregulation of Foxp2 in the R6/1 mouse is strongly correlated with alterations in impulsivity, decreased aggressive behavior, hyper-activity and several early biochemical changes. Moreover, overexpression of Foxp2 in the striatum of juvenile R6/1 striatum ameliorates impulsive-behavior displayed by R6/1 mice respect to control WT littermates and rescue their spine loss detected in medium spiny neurons.

Our data suggest that FoxP2 is one of the major and early targets for the mutant huntingtin which leads to an altered maturation striatal neuronal populations in HD that finally culminate in the appearance of pre-symptomatic psychiatric symptoms. Understanding the contribution of Foxp2 in HD could lead us to propose a comprehensive molecular mechanism with its associated circuit underlying major psychiatric symptoms in pre-symptomatic HD patients.

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PS4-60

Parvalbumin interneurons and perineuronal nets in the hippocampus and retrosplenial cortex of a murine double hit model for schizophrenia

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Schizophrenia (SCZ) is a multifactorial disease resulting in cognitive and emotional dysfunctions, usually appearing from late adolescence to early adulthood. Although its etiology is not fully understood, early life aversive experiences and alterations in neurodevelopment are considered predisposing factors. Certain brain regions such as the prefrontal cortex and the hippocampus known to be affected by early life stress are also altered in SCZ. Different reports have also described alterations in the retrosplenial cortex (RSC). Studies in patients and animal models of SCZ have found alterations in the parvalbumin (PV) expressing interneurons, making them good candidates to study the mechanisms underlying this psychiatric disorder. Some of the alterations observed in PV+ interneurons may be mediated by perineuronal nets (PNNs), specialized regions of the extracellular matrix, which frequently surrounding these inhibitory neurons. In the present study, we have used a murine double hit model combining a single perinatal injection of an NMDAR antagonist (MK801) to slightly disturb early postnatal development and post-weaning social isolation as an early life aversive experience. We have investigated the effect of the model and each of its factors on the subpopulation of PV expressing interneurons and PNNs in the hippocampus and RSC of adult male mice, using unbiased stereology. In the CA1, but not in the CA3 region of the hippocampus, the number of PNNs and PV+PNN+ cells was affected by the treatment with MK-801. In the RSC, we observed a significant impact of isolation, treatment with MK-801, and the interaction of both interventions on the number of PV expressing interneurons, PNNs, and PV+PNN+ cells. The present double-hit model constitutes a useful tool to investigate the effects of early life aversive experiences and the biological basis of schizophrenia. Our results may constitute the basis for further studies on PV expressing interneurons and the PNNs in this disorder.

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PS4-61

Thalamus reticular nucleus alterations in response to peripubertal stress in female and male mice

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Early exposure to stressful events is known to be a cause for alterations in neural development. These changes can be maintained during adult life, leading to stress-related psychiatric disorders. The thalamus reticular nucleus (TRN) is a GABAergic nucleus mostly formed by parvalbumin positive interneurons. This nucleus receives collateral glutamatergic projections form both corticothalamic and thalamocortical neurons and exerts a strong inhibition towards the thalamus. Although it is mainly known for regulating the informational flow between the cortex and the thalamus, it has also been related with the pathology of some psychiatric disorders, including some in which stress acts as a precipitating or predisposing factor. In this study we used a peripubertal unpredictable chronic stress model in mice, based on psychogenic stressors, to assess whether aversive events during peripubertal development lead to changes in the structure and connectivity of the TRN. This model has been previously used in our laboratory to recreate the effects of early stress in the prefrontal cortex, showing interesting and differential results between female and male mice. In the present study, we analyzed some molecules expressed in the TRN and related to interneuronal plasticity and the closure of critical periods, such as components of perineuronal nets and PSA-NCAM. In addition, we are analyzing other parameters related to the connectivity of the TRN with the cortex and the rest of thalamic nuclei. We intend to find some insight in the effects that adverse experiences during early life have on the development and connectivity of the TRN. This may lead to an advance on the knowledge of the neurobiological basis of some psychiatric disorders in which early-life stress acts as a predisposing factor.

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PS4-62

THE EFFECT OF NEUROTROPHIC FACTORS ON THE CEREBELLAR DESTRUCTURATION ASSOCIATED WITH AUTISM SPECTRUM DISORDERS

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Autism spectrum disorder (ASD) is an abnormal neurodevelopmental process characterized by a central symptomatology. The cerebellum is a key structure in the study of ASD for both its motor function and its involvement in cognitive, affective and social behaviour. Patients with ASD have a specific loss of Purkinje cells, together with an affectation of neurotrophic factors (NF), which also causes neuronal alterations.

This work aims at studying the social conditions present in ASD and related with cerebellum, employing the PCD mutant mouse, an animal model that presents a specific loss of Purkinje cells. For the analysis of the relationship between NF and cerebellar destructuration, both gene and protein expression of NF, such insulin growth factor 1 (Igf-1), vascular endothelial growth factor A and B (Vegf-A and Vegf-B) and brain-derived neurotrophic factor (Bdnf) were analysed at different ages: P10, P15, P20, P25, P30 and P40 (i.e. before and during the Purkinje cell loss).

Our preliminary results demonstrated a statistically significant increase in both gene and protein expressions of Igf-1 at P25 and P40, and Vegf-B at P15 and P20 in the cerebellum of PCD mice, while the other NF remained similar to control mice. In addition, the pattern of expression of Igf-1 and Vegf-B resulted radically different amongst genotypes: in wild type mice we observed oscillations in their expression, being higher at P20 and P30, while in PCD mice we did not observe that, but a constant increase of these NF. These fluctuations seem to be important for proper cerebellar function and development, whereas the increase may be related to an attempt to neuroprotection in front neuronal death.

Finally, these data have been used to carry out a pharmacological treatment with neuroprotective factors, which is currently underway.

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PS4-63

DETECTION OF BACTERIAL LIPOPOLYSACCHARIDE AND TRANSPORT MECHANISMS IN THE PREFRONTAL CORTEX OF ALCOHOL BINGE DRINKING-EXPOSED RATS

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Alcohol binge drinking (ABD) induces neuroinflammation in the prefrontal cortex of rats and damages the intestinal barrier allowing the entry of bacterial products, such as the endotoxin lipopolysaccharide (LPS), to the systemic circulation, which strongly activates the innate immune system. LPS is a big molecule and its being accepted it could not entry the brain. New evidences indicate that parts of the LPS such as Lipid A and core could reach the brain in physiological conditions by binding to specific apolipoproteins. However, the infiltration in the brain and the transport mechanisms have not been explored in ABD conditions. Here, we explored the presence of the endotoxic component of LPS, the Lipid A, in frontal cortex of rats exposed to ABD and study the mechanisms of transportation by binding to apolipoproteins ApoA1 and ApoB in male and female rats.

Animals were exposed to intragastric binge ethanol administrations (3 times/day x 4 days) with a maximum dose of 3 g/kg of ethanol in a solution of 30 percent (w/v). To verify intoxication, blood ethanol levels were determined in blood samples taken from tail. Female reproductive cycle was controlled by taking vaginal secretion once a day and microscopic analysis. Free ApoA1, ApoB and Lipid A levels and binding (Apo-Lipid A) aggregates were measured by western blot analysis and confirmed by Co-Immunoprecipitation.

Results indicate that neither free Lipid A nor ApoA1 and ApoB are increased in the frontal cortex of ABD male or female rats compared to controls. However, significant increases in the Lipid A / ApoA1 and Lipid A / ApoB ratios were observed in this structure, indicative of the binding of Lipid A with these apolipoproteins, as confirmed by Co-Immunoprecipitation.

Our results suggest that LPS infiltrates the brain in ABD conditions through a lipoprotein transport mechanism which does not show sexual differences.

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PS4-64

UPREGULATION OF TLR4 SIGNALLING PATHWAY AND BEHAVIORAL DISHINIBITION IN WERNICKE-KORSAKOFF SYNDROME: EVIDENCE FROM AN ANIMAL MODEL AND HUMAN POST-MORTEM TISSUE

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Wernicke-Korsakoff syndrome (WKS) is a neuropsychiatric disorder induced by thiamine deficiency (TD) whose main causal factor is alcoholism. WKS patients show significant mood and executive function alterations which are even more devastating than memory problems. A dysfunction in the prefrontal cortex (PFC) has been associated to impulsivity and disinhibition in WKS patients. This pathology occurs with neuroinflammation as one of the mechanisms responsible of brain damage, but specific mechanisms have not been understood yet. Here, we explored the innate immune receptor Toll-like 4 (TLR4) and its signaling pathway in postmortem human tissue and in a WKS animal model and its relationship with behavioral disinhibition.

WKS was induced in rats by chronic consumption of 20% (w/v) alcohol during 9 months along with a TD hit (TD diet + pyrithiamine 0.25 mg/kg, i.p. daily injections) during the last 12 days of experimentation. Rats were evaluated on behavioral tasks that are highly dependent on the PFC, as the elevated plus maze and open field test at the end of treatments. Rat PFC was dissected and analyzed for TLR4, MyD88, IκBα and HSP70 expression. Additionally, immunohistochemical studies were carried out in postmortem brain of an alcohol-induced WKS diagnosed subject.

WKS animals showed a clear disinhibited-like behavior, which correlated with the upregulation of the TLR4 signaling pathway in the PFC. Interestingly, postmortem PFC samples of a WKS diagnosed patient showed an upregulation of TLR4 and its co-receptor MyD88 both in gray and white matter structures compared with a paired healthy control.

Our results show alterations in the TLR4 pathway in WKS postmortem human brain and suggest a key role for cortical TLR4 in the disinhibition-like behavior, as evidenced by the WKS animal model.

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PS4-65

Non-motor symptoms and neuronal alterations in a comorbidity mice model of depression and Parkinson's disease

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Parkinson´s disease (PD) is the second more prevalent neurodegenerative disease. Besides motor impairments, increasing evidences demonstrate the presence of non-motor symptoms co-morbid with PD. Some of these symptoms can appear at early stages of the disease and may worsen the pathology, resulting in a poorer quality of life. One of the most common and disabling co-morbidities are the emotional alterations, such as anxiety and depressive symptoms, present in more than 50% of PD patients. The neuronal alterations that cause motor symptoms in PD are well characterized, thanks to the availability of several models that successfully reproduce them. In contrast, comorbid PD models that recapitulate the non-motor symptoms to study the neuronal alterations involved are not available. Beyond dopamine decline, there are other monoaminergic systems altered in PD, such as serotonin or noradrenaline. The dorsal raphe nucleus and the locus coeruleus, respectively the main serotonin and noradrenalin source of the brain, are affected at early stages of PD, when the emotional symptoms appear. The altered activity in these nuclei and in their projection fields may be involved in the pathophysiology of these mental comorbidity. In this work, we used the aphakia mice, a genetic PD model induced by the down-regulation of the Pitx3 transcription factor, that triggers a failure in the nigro-striatal dopaminergic pathway and a moderate parkinsonian phenotype, mimicking mild stages of PD, when emotional symptoms appear. We aim to, first, stablish the aphakia mice as a parkinsonian model with mental comorbidities and, second, define the neuronal circuits involved in the appearance of anxiety and depression. We found that the aphakia mice show anxiety and depressive signs associated with a decreased number of dopamine neurons in the DRN and decreased catecholaminergic transmission in the projection fields.

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PS4-67

STEREOLOGICAL ANALYSIS OF NEURONS AND GLIA IN THE SUBICULAR COMPLEX IN ALZHEIMER'S DISEASE

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Alzheimer´s disease (AD), the most prevalent neurodegenerative disorder worldwide, is clinically characterized by cognitive deficits. Neuropathologically, deposits of amyloid-β and tau proteins accumulate in the brain in a six-stages predictable pattern. These misfolded proteins can propagate cell-to-cell in a prion-like manner and induce native proteins to become pathological.

Neuronal loss and volume reduction in entorhinal cortex (EC) and hippocampus (HP) have been largely reported, key regions in both the onset of the disease and the cognitive deficits observed in AD patients. In this sense, the subicular complex (SC) is a region of special interest because it represents the connecting bridge between the EC and the HP. However, the role of the SC in AD remains to be elucidated. Therefore, the aim of this work has been to quantify the volume and stereologically analyze neuronal and glial changes within the human SC including subiculum, presubiculum and parasubiculum.

Experimental procedures were approved by the Ethical Committee of Clinical Research at Ciudad Real University Hospital (SAF2016-75768-R). Post-mortem human brain samples were provided by the Spanish Biobank Network. Two experimental groups were used: n=9 AD cases (stages V/VI) and n=9 age-matched non-AD cases. Volumetric quantification of SC was performed using Cavalieri method. Neurons (Neu-N), microglia (Iba-1) and astroglia (GFAP) were also quantified by optical fractionator method using immunohistochemical staining.

Volumetric changes and differential involvement of neural and glial populations by proteinopathies in the SC could help to understand how cortical circuitry is involved in the spreading throughout the medial temporal lobe.

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PS4-68

ROS-INDUCED SP1 REGULATES WRAP53 LEVELS AND NUCLEAR ACCUMULATION LEADING TO NEUROPROTECTION AFTER ISCHEMIA

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Ischemia-induced oxidative stress compromises genome integrity, which results in DNA damage and neuronal loss after stroke. We described that reactive oxygen species (ROS) generated during ischemia upregulate WRAP53 (WD40 encoding RNA antisense to p53) and trigger its translocation to the nucleus, where it promotes DNA repair [1]. However, the molecular mechanism remains unknown. Transcription factor Sp1 acts as a pleiotropic oxidative stress response protein in neurons. Particularly, ROS-induced Sp1 expression promotes neuroprotection against ischemia [2]. Interestingly, Wrap53 promoter contains putative consensus sequences (GC boxes) for Sp1. We analyze the role of Sp1 as a modulating factor of WRAP53-mediated neuronal survival and its impact on brain repair after stroke.

Primary cortical neurons were subjected to in vitro ischemia (oxygen and glucose deprivation, OGD). Levels of WRAP53 and Sp1 were modulated by lipofection with plasmids and siRNA. Protein location and 53BP1 foci formation (DNA repair marker) were analyzed by immunofluorescence. For in vivo experiments, mice were subjected to middle cerebral artery occlusion (MCAO), a validated model of cerebral ischemia.

We found that ischemia rapidly induced Sp1 expression in neurons, which preceded WRAP53 accumulation. Sp1 and WRAP53 accumulated in the nuclei after OGD, which was confirmed in vivo. By ChIP assay on SH-SY5Y cells, we found that the GC boxes-containing Wrap53 promoter region co-immunoprecipitated with anti-Sp1, suggesting Sp1 as a modulator of WRAP53 expression. Interestingly, Sp1 downregulation by siRNA prevented WRAP53 upregulation and nuclear translocation induced by OGD in neurons, leading to inactivation of DNA repair response and neuronal death.

Sp1 modulates WRAP53 expression and nuclear accumulation after ischemia through a ROS-dependent pathway. This new ROS-Sp1-WRAP53 signaling pathway poses Sp1 and WRAP53 as attractive targets for new neuroprotective strategies in ischemic stroke.

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PS4-69

THE VPA MURINE MODEL OF AUTISM: DIFFICULTIES AND ACHIEVEMENTS RELATED TO ITS OBTAINMENT AND ANALYSIS

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Autism is a neurodevelopmental disorder with a multifactorial origin and diverse manifestations. Although many progresses have been made in the knowledge of this condition, there is still a long way to understand its cellular, neuroanatomical, and behavioural bases. In addition, it is mandatory to explore possible treatments that might ameliorate the symptomatology of people with this disorder. In this sense, biomedical research using animal experimentation has generated significant advances in the knowledge of autism. Nowadays several animal models that mimic autism in humans are used, either generated from exposure to environmental factors or carrying identified human genetic mutations.

One of the most validated and worldwide employed animal models for autism research is the valproic acid-induced rodent model of autism (VPA). However, we have detected multiple difficulties to obtain it and, unfortunately, the existing literature does not expose these arising hindrances. In the present work we describe the path that our team followed to generate the VPA model. Several problems emerged related to difficulties on the set of the optimal dosage of valproic acid: sedative and/or epileptogenic signs in dams, abortion in pregnant mice and mortality in dams and offspring.

Once solved these obstacles, we started to investigate the olfactory bulb histopathology of the animal model by histochemistry and immunohistochemistry, and its olfactory capabilities through a variation of the Marble Burying Task using odorants. Our preliminary results suggest variations at both levels in the VPA model. The analysis of the olfactory system will shed light on the autism spectrum disorders research field, as it has been shown that the sensory alterations in this condition could be affecting its general pathogeny.

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PS4-70

Immature oligodendrocytes with R-Ras1 and R-Ras2 deficiency produce axonal degeneration

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Fast synaptic transmission in vertebrates is critically dependent on myelin for insulation and metabolic support. Myelin is produced by oligodendrocytes that maintain multilayered membrane compartments that wrap around axonal fibers, and alterations in myelination can therefore lead to severe pathologies such as multiple sclerosis. Given that hypomyelination disorders have complex etiologies, reproducing clinical symptoms of myelin diseases from a neurological perspective in animal models has been difficult. We recently reported that R-Ras1-/- and/or R-Ras2-/- mice, which lack GTPases essential for oligodendrocyte survival and differentiation processes, present different degrees of hypomyelination in the Central Nervous System with a compounded hypomyelination in double knockout (DKO) mice. Here, we discovered that R-Ras1 and/or R-Ras2 loss of function is associated with aberrantly myelinated axons with increased numbers of mitochondria and a disrupted mitochondrial respiration that leads to increased ROS levels. As a consequence, aberrantly myelinated axons are thinner with cytoskeletal phosphorylation patterns typical of axonal degeneration processes characteristic of myelin diseases. Although we observed different levels of hypomyelination in single mutant mice, the combined loss of function in DKO mice lead to a compromised axonal integrity triggering a loss in visual function. Our findings demonstrate that R-Ras loss of function reproduces several characteristics of myelin diseases, and we therefore propose that R-Ras1-/- and R-Ras2-/- neurological models are valuable approaches for the study of myelin pathologies.

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PS4-71

Inflammation And Autophagy In Glycogen-Induced Neurodegeneration

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Lafora disease (LD) is a fatal childhood-onset dementia characterized by the extensive accumulation of glycogen aggregates—the so-called Lafora Bodies (LBs)—in several organs. The accumulation of LBs in the brain underlies the neurological phenotype of the disease. LBs are composed of abnormal glycogen and various associated proteins, including p62, an autophagy adaptor that participates in the aggregation and clearance of misfolded proteins. Our results demonstrate that p62 participates in the formation of LBs and suggest that the sequestration of abnormal glycogen into LBs is a protective mechanism through which to reduce the deleterious consequences of its accumulation in the brain (1).

Until recently, it was widely believed that brain LBs were present exclusively in neurons and thus that LD pathology derived from their accumulation in this cell population. However, we have demonstrated that LBs are also present in astrocytes. Strikingly, impeding LB accumulation in astrocytes prevents the increase in neurodegeneration markers, autophagy impairment, and metabolic changes characteristic of LD in a mouse model. Conversely, mice that overaccumulate glycogen in astrocytes show an increase in these markers. These results unveil the deleterious consequences of the deregulation of glycogen metabolism in astrocytes and change the perspective that LD is caused solely by alterations in neurons (2).

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PS4-72

Age-dependent multisystem parkinsonian features in a novel neuromelanin-producing transgenic mouse model

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Parkinson's disease (PD) is characterized by a preferential degeneration of neurons that accumulate with age the pigment neuromelanin, especially neurons from substantia nigra (SN) and locus coeruleus (LC). We aim to characterize the consequences of age-dependent intracellular neuromelanin accumulation in catecholaminergic neuronal populations to understand the relationship between this process and the vulnerability of these cells in PD, as well as its impact on healthy brain aging. We previously generated a rat model exhibiting progressive unilateral SN production of neuromelanin that showed parkinsonian-like neuropathology and motor deficits1. Here, we generated a new neuromelanin-producing rodent model, based on the tissue-specific constitutive expression of human tyrosinase (hTyr) under the tyrosine hydroxylase (TH) promoter (Tg-TH-hTyr), that mimics the bilateral distribution of pigmentation within the aging human brain (i.e. catecholaminergic groups A1-A142). In parallel to neuromelanin intracellular buildup, Tg-TH-hTyr mice exhibited major PD features, including motor and non-motor behavioral alterations, inclusion body formation and degeneration of specific catecholaminergic neuronal groups. Genome-wide transcriptomic analysis of neuromelanin-laden neurons revealed alterations in PD-related biological pathways that correlate with human PD postmortem studies. Our results show that modelling human neuromelanin accumulation in rodents leads to age-dependent catecholaminergic dysfunction and molecular alterations resulting in motor and non-motor deficits, which is relevant to PD pathology and brain aging.

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PS4-73

DIAZEPAM ADMINISTRATION IN THE INTRAHIPPOCAMPAL KAINIC ACID ANIMAL MODEL OF EPILEPSY RESCUE BRAIN FDG-PET HYPOMETABOLISM IMAGING

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2-deoxy-2-(18F)fluoro-D-glucose in positron emission tomography (FDG-PET) is an efficient tool to characterize the changes in brain glucose metabolism, in which hypometabolism seems to be an early marker of epileptogenesis since it is associated with neuronal death and inflammatory processes. In animal epilepsy models, diazepam is usually administered after the status epilepticus in order to prevent high rate mortality. The aim of this study is to determine whether the administration of diazepam can modify the metabolic or neurohistochemical characteristics related to the intrahippocampal kainic acid (KA) animal model of epilepsy.

Intrahippocampal kainic acid surgery was carried out in 21-day-old male C57BL/6J mice, followed or not by diazepam (10 mg/kg, i.p.) administration. Static FDG-PET studies were performed before surgery (baseline measure), 24 hours and 7 days after surgery. Brains were extracted on day 8 to measure neurodegeneration (FluoroJadeC), neuroinflammation (GFAP, Iba1) and neuronal death (activated Caspase 3, Nissl) by neurohistochemistry.

FDG-PET neuroimaging showed differences in the dynamics of brain metabolism over time. The use of diazepam attenuates the hypermetabolism generated by KA 24 hours after surgery, reaching levels similar to the group without epilepsy. Furthermore, the epilepsy group without diazepam administration showed marked hypometabolism at 7 days, contrary to the group with diazepam. At the neurohistochemical level, differences in inflammation, neurodegeneration and neuronal death were observed even with the administration of diazepam.

In conclusion, diazepam in this model has an effect at the metabolic level, rescuing the differences that occur in the model without diazepam, so its use should not be recommended when the aim of the research is to use FDG-PET as a diagnostic tool in this model, although the neurohistochemical correlate associated with this disorder is maintained.

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PS4-74

Activation of SGK1.1 up-regulates the M-current in presence of epilepsy mutations

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In the central nervous system, the M current plays a critical role in regulating the subthreshold electrical excitability of neurons, determining their firing properties and responsiveness to synaptic input. M-channel is mainly formed by subunits Kv7.2 and Kv7.3 that co-assemble to form a heterotetrametric channel. The relevance of their functionality is demonstrated by the negative effects of mutations on their encoding genes. Mutations in KCNQ2 and KCNQ3 have been associated with a long list of hyperexcitability phenotypes including benign familial neonatal epilepsy (BFNE) and neonatal epileptic encephalopathy (NEE). SGK1.1, the neuronal isoform of the serum and glucocorticoids-regulated kinase 1 (SGK1), is a M-current modulator described by our group able to increase M-current density in neurons, leading to reduced excitability and protection against seizures. Herein, using two-electrode voltage clamp on Xenopus laevis oocytes, we demonstrate that activated SGK1.1 is able to up-regulate the M-channel in presence of two different epilepsy mutations found in Kv7.2 subunit, R207W and A306T. In addition, proximity ligation assays on N2a cell line allowed us to address the effect of these mutations on Kv7-SGK1.1-Nedd4 molecular associations, a proposed pathway underlying the M-channel up-regulation by SGK1.1

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PS4-75

STAT3 inhibition prevents the transformation of NSCs into Reactive-NSCs in epilepsy

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Adult neurogenesis persists throughout adulthood in the hippocampus of most mammals because of a population of neural stem cells (NSCs) that remains in the dentate gyrus. The capability of NSCs to generate neurons is promoted by neuronal activity. However, hyperexcitation at the level of epileptic seizures induce NSCs to transform into reactive NSCs (React-NSCs), that become multibranched and hypertrophic and abandon neurogenesis to enter massively in mitosis and transform into reactive astrocytes that contribute to gliosis. We are now exploring signaling mechanisms that control the transformation of NSCs into React-NSCs.

One of the candidates is STAT3 (signal transducer and activator of transcription 3) which plays a critical role in astrogliogenesis and NSCs proliferation and differentiation. We have confirmed by quantitative rtPCR (Q-rtPCR) that STAT3 is overexpressed and by confocal microscopy that the phosphorylated form (P-STAT3) is increased in React-NSCs in a mouse model of mesial temporal lobe epilepsy (MTLE). Further we have stablished a model of React-NSCs in culture, which allows an easier manipulation of the STAT3 activity. We have confirmed also by Q-rtPCR and by confocal microscopy that these cultured React-NSCs also overexpress STAT3 and have more P-STAT3 when compared to control NSCs.

We hypothesize that the inhibition of STAT3 activity will prevent the induction of React-NSCs. To test this hypothesis, we are using two strong inhibitors of STAT3 activity: pharmacological agent WP1066 and silibinin, the main component of silimarin which is isolated from the seeds of milk thistle (Sylibum marianum). Our preliminary results suggest that indeed the inhibition of STAT3 reduces the transformation of NSCs into React-NSCs, as it decreases their overproliferation as well as their morphological transformation.

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PS4-76

Role of the NMDAR-NR2B subunits in the function of supramolecular NMDAR-BK complexes.

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Large conductance calcium- and voltage-activated potassium channels (BK) are widely expressed across many tissues, contributing to many physiological functions. Membrane depolarization and relatively high (micromolar) intracellular concentrations of Ca2+ are required for their activation. Such concentrations are reached in the vicinity of Ca2+-permeant ion channels, to which BK proteins are closely located in various tissues, including the brain. N-methyl-D-aspartate receptors (NMDAR) are sodium (Na+)- and Ca2+-conducting glutamate-activated ion channels that are functionally coupled to BK channels in the olfactory bulb and the dentate gyrus (Isaacson et al., 2001; Zhang et al., 2018), contributing to decreased neuronal intrinsic excitability. Recently, we have shown that postsynaptic NMDAR-BK complexes at basal dendrites of somatosensory cortex layer 5 pyramidal neurons regulate synaptic transmission and long-term plasticity. However, the specific contribution of different NMDAR subunits (NR1 and NR2A/NR2B) to the NMDAR-BK interaction remains elusive. Defects in this association may be of pathological relevance in the context of syndromes MRD6 (mental retardation, autosomal dominant 6) and EIEE27 (epileptic encephalopathy, early infantile, 27), which have been related to mutations in the NR2B-encoding gene (GRIN2B).
In this work we aimed to understand the role of NR2B subunits in the function of NMDAR-BK complexes and, more specifically, if NR2B-related human mutations modify NMDAR-BK coupling. Function of NMDAR-BK complexes containing different MRD6- and EIEE27-related NR2B mutations was tested using electrophysiology in heterologous expression systems. Proximity between channel proteins within complexes was assessed using in situ proximity ligation assays (PLA). Our results reveal some disease-related NR2B mutations that reduce the NMDAR-BK interaction, either by altered interactions with the BK channels and/or by functional uncoupling between the channels within the NMDAR-BK complexes.

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PS4-77

FAIM-L as a modulator of Tau-pathology in Alzheimer's disease and other tauopathies

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Alzheimer's disease (AD) is characterized by two main biological hallmarks: beta-amyloid aggregates and the formation of intracellular neurofibrillary tangles (NFTs). NFT formation is linked to neuronal death and cognitive dysfunction. NFTs are composed of abnormally hyperphosphorylated and aggregated Tau protein. Tau, a MAPT protein, is essential to maintain molecular dynamics in mature neurons. Aberrant modifications of Tau, such as phosphorylation, are associated with a reduction in Tau functionality, the formation of the aforementioned NFTs, and the consequent neuronal death. Our laboratory has been focused in the study of the Fas apoptotic inhibitory molecule (FAIM-L). FAIM-L is an anti-apoptotic protein only expressed in neurons. It has also been involved in non-apoptotic functions such as neuronal pruning and axonal degeneration. We have previously reported that FAIM-L is reduced in AD patients and in the APPxPS1 mice model.

In the present study, we show that FAIM-L is only reduced in mice models that show Tau pathology, such as P301S and VLW mice. Other AD models, which only present beta-amyloid pathology, do not present FAIM-L downregulation. In P301S mice, FAIM-L reduction is observed previously to synaptic deficits (3 months) or extensive neurodegeneration (9 months).The mechanism by which aberrant Tau could be reducing FAIM-L levels needs further investigation. Here, we demonstrate an interaction between Tau and FAIM-L and propose that this reduction could be dependent of Tau phosphorylation status. We hypothesize that FAIM-L reduction may enhance the Tau-associated pathology. Using AAVs we aim to overexpress FAIM-L in hippocampus of P301S mice and determine the effect of restoration of FAIM-L levels in the progression of the disease. With this work would like to establish FAIM-L as a possible new therapeutic target in AD and other Tau-related neurodegenerative diseases.

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PS4-78

The overexpression of NRG1-type III does not ameliorate ALS clinical outcome in hSOD1G93A mouse model.

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Amyotrophic Lateral Sclerosis (ALS) is an adult onset disease that affects motor neurons (MNs) in the cerebral cortex, brainstem and spinal cord. Most of ALS cases (~90%) are sporadic, but ~10% of the cases are inherited. In approximately 20% of familial cases, the disease is caused by mutations in the gene encoding Cu/Zn-superoxide-dismutase1 (SOD1). Transgenic rodents overexpressing this mutated gene develop a neuromuscular disorder similar to human ALS.

Afferent inputs to MNs are crucial in regulating their excitability. Among different types of synaptic afferents, MNs receive prominent cholinergic C-type ("C-bouton") inputs from spinal interneurons. C-boutons modulate MN excitability, and synaptic transmission throughout C-boutons is involved in the regulation of MN vulnerability.

Some C-bouton-associated molecules appear to be relevant in ALS, like the sigma 1 receptor (S1R) (which mutations cause a juvenile familial form of ALS and its pharmacological activation prolongs lifespan of SOD1G93A mice) or the NRG1 receptor ErbB4 (which mutation causes another type of FALS). We have previously observed that neuregulin-1 (NRG1) accumulates in C-boutons, and described C-bouton alterations in a mouse model of ALS.

NRG1 signaling has been directly targeted in SOD1-ALS mice by virus-mediated delivery of NRG1 typeIII to the spinal cord, resulting in extended survival time and reduced C-bouton loss, and gene therapy based on intrathecal administration of adeno-associated virus to overexpress NRG1-III in SOD1G93A mice has therapeutic role.

By cross-breeding hSOD1G93A mice and NRG1-type III overexpressor mice (transgenic mice overexpressing human influenza hemagglutinin [HA])–tagged full-length NRG1 typeIII [HA-NRG1FL]), we created here a double transgenic mouse line. In this, we examined changes in body weight and survival, and performed behavioral and histopathological studies in spinal cord and skeletal muscles showing no improvement in either motor phenotype or lifespan. Our results indicate that the endogenous overexpression of NRG1-typeIII the does not ameliorate the SOD1G93A mouse phenotype.

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PS4-79

Generation and characterization of human pluripotent stem cell (hPSC)-derived astrocytes to model Alzheimer´s disease.

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Alzheimer disease (AD) is characterized clinically by memory loss and pathologically by amyloid-β (Aβ) accumulation, neurofibrillary tangle formation, extensive neuroinflammation, synaptic toxicity and neurodegeneration. Recent studies highlight the importance of glial cells on the pathogenesis and progression of AD. Among glial cells, astrocytes are fundamental for maintaining homeostasis and protecting neurons but, under different pathological conditions, when stimulated by specific factors, acquire different activation states that can be protective or harmful. While it is well established that astrocytes undergo profound alterations in gene expression, morphology and function during the course of AD, such changes are still poorly defined and mostly unknown in the case of human astrocytes.

To analyze human astrocyte reactive states in the context of AD, we are using the stem-cell technology to generate astrocytes derived from human pluripotent stem cells (hPSCs) and in vitro models of AD in which astrocytes are exposed to various Aβ challenges. Human astrocyte identity as well as reactivity after Aβ stimulation are being characterized at molecular and functional levels with various assays.

hPSC-derived astrocytes at day in vitro 90 express main markers of astrocytes (GFAP, S100, EAAT1, EAAT2, Vimentin and AQP4) without expression of neuron (MAP2) and oligodendrocyte (O4) markers. After stimulation with oligomeric Aβ, hPSC-derived astrocytes show a reactive profile that we are characterizing.

In sum, our approach allows exploration of the human astrocyte reactivity on an AD context and will provide insights into the contribution of astrocytes to the pathophysiology of AD.

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PS4-81

The Gut-Brain Axis in a novel humanized transgenic mouse model for Parkinson´s disease and brain aging

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Accumulating genetic, epidemiological, neuropathological and clinical data indicate that alterations in the gastrointestinal (GI) function and the gut microbiota represent a risk factor for Parkinson's disease (PD). Changes in the bidirectional communication between the gut and the brain can affect both the enteric nervous system and the central nervous system, which might have important implications in understanding disease pathophysiology and for the development of disease modifying therapeutic strategies. However, the precise molecular mechanisms underlying this bidirectional communication in the context of PD are not fully understood.

In order to clarify how GI dysfunction is involved in disease pathogenesis and/or in modulating the manifestation of PD symptoms, we have characterized the GI function and the key mechanisms involved in the gut-brain axis of a new humanized transgenic PD mouse model (Tg-Th-hTyr). This model is based in the progressive accumulation of neuromelanin in all catecholaminergic nuclei of the brain, including the dorsal motor nucleus of the vagus nerve innervating the GI system. We have performed a battery of motor and non-motor behavioral tests to assess the phenotype of these animals, including the GI function. In addition, we have evaluated gut dysbiosis in fecal samples by 16S RNA gene sequencing and intestinal inflammation using cytokine profiling and histological examination of Tg and wild-type (wt) littermates.

Our results show impaired motor activity in Tg mice compared to wt littermates at 6 months of age. We also detected increased fecal output in Tg mice placed in a novel environment, suggesting alterations in the hypothalamic-pituitary-adrenal (HPA) axis. In the same line, we observed a significant increase in body weight and water/food intake in Tg mice. Our results indicate that the gut-brain axis is altered in neuromelanin-producing transgenic mice and that this novel PD model can contribute to clarify the role of gut dysfunction in PD pathogenesis.

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PS4-82

Purification and characterization ofhPSC-derived striatal progenitor subpopulations for transplantation in Huntington's Disease

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Huntington's disease (HD) is a currently incurable neurodegenerative disease primarily characterized by the loss of medium spiny neurons in the striatum. Cell replacement therapy is the only approach currently focused on structural and functional restoration of atrophied tissue in HD by replenishing the degenerating MSN population.

Human pluripotent stem cell (hPSC)-derived neural progenitors can relieve motor deficits in animal models of HD; however, clinical translation of protocols is still limited by the heterogeneity of cell products. Cell sorting is considered instrumental to ensure reproducible generation of defined cell products. Here, we describe that marker X is a cell surface marker suitable for enrichment of hPSC-derived striatal neuroblasts.

Based on this, we have successfully set up and optimized an immunomagnetic sorting pipeline which allows for high-yield enrichment of striatal neuroblasts in heterogenous cell populations resulting from in vitro differentiation. We have demonstrated that the implementation of this approach leads to a reduction of not only the heterogeneity of the final cell product, but also of batch-to-batch variation in both control and HD cell lines. Furthermore, we have proved the versatility of our strategy showing that different neuroblast subtypes can be enriched under different conditions.

Selected neuroblasts from control and HD cell populations have been characterized in vitro in terms of their identity and potential to generate different neuron subtypes after striatal differentiation. Furthermore, we have transplanted these neuroblasts into the striatum of adult mice and observed evidence of their in vivo survival and integration into the striatum up to one-week post transplantation.

In conclusion, we anticipate that X-based cell sorting prior to transplantation has the potential to enable the development of safer and more reproducible cell products to be used for clinical cell replacement strategies in HD.

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PS4-83

Unravelling the distribution and function of the lipid transfer protein VPS13A in the brain to understand chorea acanthocytosis pathology

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Chorea-acanthocytosis (ChAc) is caused by a VPS13A gene mutation leading to marked reduction or absence of VPS13A protein. ChAc patients show progressive movement disorders such as chorea and dystonia. The main neuropathologic feature in VPS13A mutations is a selective degeneration of the striatum, however, little is known about the VPS13A expression in the brain. There is also a poor knowledge about VPS13A function in neural cells. Thus, the objectives of this work are a) to assess the time course and the regional expression of vps13a gene in the mouse brain and b) to study the vps13a interaction partners. Single cell RNA showed that vps13a is present in mature neurons and qPCR revealed that vps13a expression is stable over time. Then, we used fluorescence in-situ hybridization and immunohistochemistry to determine the distribution of vps13a mRNA and protein in mouse brain from embryonic stages to adulthood. In the adult mouse brain, we found a widespread distribution of vps13a, with different staining intensity profiles between nuclei. In general, the mRNA localization resembled that of the protein one with an enrichment in the pons, cerebellum and hippocampus. We found moderate staining in the cortex and in the most thalamic and hypothalamic nuclei. Interestingly, we found weak staining in the basal ganglia nuclei. We observed vps13a staining in glutamatergic, GABAergic and cholinergic neurons. Not only neurons but also some glial cells expressed chorein. The levels of vps13a protein were not modulated neither by pilocarpine, amphetamine nor ketamine treatments, suggesting that VPS13A has structural and stable role in neural cells. We also evaluated the vps13a interactome through a specific protein immunoprecipitation from mouse cerebral cortex followed by mass spectrometry. Vps13a interacts with lipid metabolism proteins. Understanding the brain tissue distribution, expression and protein interacting partners can provide novel insights toward the knowledge of ChAc pathophysiology.

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PS4-84

Progressive behavioural, biochemical and microbial changes during different stages of stress

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Major depression (MD) is a common, relapsing mental illness that affects millions of people worldwide. One of the most studied risk factors associated with MD is chronic stress. Current treatment is ineffective in 30% of patients so there is a need to fully understand the pathophysiology of MD. The role of the microbiota-gut-brain axis in regulating stress-response is emerging as a particular area of interest.

Here, we want to evaluate if the changes induced by stress are accumulative and time dependent. To do so, we divide our mice into control non-stressed (NS), short-term stress mice (STS) and long-term stress mice (LTS). STS mice received only two days of stress whereas LTS mice underwent the chronic unpredictable mild stress protocol (CUMS) for 28 days. After the stress protocol, we analyse the biochemical, behavioural, and microbial changes induced by stress.

Results indicate that LTS induces much more severe depressive-like symptoms than STS as demonstrated in the body weight, the fur appearance, and in the anxiety levels in the open field. Moreover, biochemical analysis reveals huge differences depending on the duration of the stress. The study of the microbiome in faeces also shows that the changes in the microbiota are mostly observed in chronically stressed mice.

In summary, our work suggests that there is a progression in the biochemical, behavioural and microbial changes induced by stress. Future work trying to restore the microbiome alterations will allow us to better understand the importance of the gut-brain axis in response to chronic stress.

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PS4-85

CHRONICALLY INCREASING CORTICOSTRIATAL ACTIVITY PRODUCES STRIATAL ASTROCYTOSIS IN MICE

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In Parkinson's disease, the neurodegenerative process of nigrostriatal cells involves the activation of striatal astrocytes. However, the possible causal relationships between striatal astrocytosis and nigrostriatal degeneration remain unclear. Here we hypothesized that striatal astrocytosis may be directly induced by excessive corticostriatal activity.

To test this hypothesis, we performed descriptive and causal experiments in wild-type mice. Our primary outcome measure was the immunohistochemical expression of glial fibrillary acidic protein (GFAP), which is a sensitive marker of striatal astrocytosis in animal models of nigrostriatal degeneration.

First, we found that the normal antero-posterior and medial-lateral organization of GFAP in the dorsal striatum corresponds to the known topography of corticostriatal projections from the sensorimotor cortex. Second, by chemogenetically manipulating corticostriatal activity with designer receptors exclusively activated by designer drugs (DREADDs), we observed that chronically increasing corticostriatal activity for 3 weeks increases GFAP expression in the receiving striatal areas.

These results suggest that excessive corticostriatal activity by itself can produce striatal astrocytosis, thus representing a possible top-down stressor in Parkinson's disease.

PS4-86

IGF-I MITIGATES POST-TRAUMATIC STRESS THROUGH OREXIN NEURONS

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Maladaptive coping behaviors are probably involved in post-traumatic stress disorders (PTSD), but underlying mechanisms are incompletely understood. We previously documented that insulin-like growth factor I (IGF-I) is associated to vulnerability to stress both in mice and humans. Since hypothalamic orexin neurons express IGF-I receptors and are involved in responses to stress, we analyzed their role in the modulatory actions of IGF-I on stress.

Anxiolytic actions of IGF-I were measured after exposure to a predator using osmotic minipumps implanted icv in mice lacking IGF-I receptors in orexin neurons (Firoc mice). Firoc mice were submitted to fear conditioning and thereafter to c-Fos immunostaining in orexin neurons and noradrenergic neurons of the locus coeruleus nucleus. Chemogenetic (DREADD) inhibition of orexin neurons was carried out in fear conditioning and in an extended protocol including context recall and anhedonia tests. Molecular changes related to PTSD were determined by qPCR at different time points. Moreover, excitatory/inhibitory (E/I) balance in orexin neurons was analyzed by immunocytochemistry.

We found that Firoc mice are unresponsive to the anxiolytic actions of IGF-I and develop PTSD-like behavior that is ameliorated by inhibition of orexin neurons. Further, systemic IGF-I treatment ameliorated PTSD-like behavior in a wild type mouse model of PTSD. In addition, systemic IGF-I increased the E/I ratio in orexin neurons of naïve wild type mice by increasing the dephosphorylation of GABA(B) receptor subunit through inhibition of AMP-kinase (AMPK). Significantly, pharmacological inhibition of AMPK mimicked IGF-I, normalizing fear behavior in PTSD mice.

Collectively, these results suggest that IGF-I enables coping behaviors by balancing E/I input onto orexin neurons in a context-dependent manner. These observations provide a novel therapeutic approach to PTSD through modulation of AMPK.

PS4-87

Estradiol Regulates PSA-NCAM Expression and Connectivity of O-LM Interneurons in The Hippocampus of Adult Female Mice

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17β-Estradiol is a sex hormone with well-reported effects on excitatory neurons and networks. However, our understanding on how this hormone affects inhibitory circuits and interneurons, namely O-LM cells, is still scarce. The somata of these cells are placed in the stratum oriens of the hippocampus and they innervate pyramidal neurons in the stratum lacunosum moleculare. They express somatostatin, display dendritic spines, and show high structural plasticity and dynamics modulated by the plasticity-related molecule PSA-NCAM. Furthermore, they contribute to the modulation of theta oscillations and receive direct input from the entorhinal cortex, altogether highlighting their importance. GIN mice are a great tool to study these neurons because they express constitutively GFP in a Golgi-like manner. Therefore, to study the effect 17β-Estradiol has on their structural plasticity and its regulation by PSA-NCAM, we used adult female ovariectomized mice of this strain. We show that the replacement treatment decreases the expression of PSA-NCAM in strata oriens and lacunosum moleculare, where these interneurons are located, as well as increases the density of inhibitory markers around these cells. Furthermore, it also increases the density of their axonal boutons, as well as lowers the density of their dendritic spines only in O-LM interneurons lacking PSA-NCAM expression. To further research these effects, we also performed entorhino-hippocampal organotypic cultures in order to image in real time these cells and study their structural dynamics being modulated by this hormone. Here we show a decrease of the appearance rate of dendritic spines, while the disappearance and stability rates remained unchanged. Altogether our results underscore the effect 17β-Estradiol has on the structural plasticity of these interneurons and how it is modulated by PSA-NCAM.

PS4-88

DISENTANGLING MICROGLIA AND ASTROCYTES ACTIVATION AND NEURODEGENERATION NON-INVASIVELY USING DIFFUSION MRI

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Neuroinflammation is emerging as a cause of the pathogenesis of neurodegenerative diseases [1-4]. Recently we proposed an innovative strategy to image microglia and astrocyte activation in grey matter using diffusion-weighted Magnetic Resonance Imaging (dw-MRI) by building a microstructural multi-compartment tissue model based on glial morphology [5]. However, the capability of the framework to tease apart inflammation with and without neuronal damage was still to be evaluated. Therefore, our objective is to probe the feasibility of the framework for characterizing the inflammatory tissue state under neurodegeneration. To this end, we used a hippocampal rat neurodegeneration model through injection of ibotenic acid where dw-MRI and immunohistochemistry data were compared.

Nine rats were injected bilaterally in the dorsal hippocampus with 1 µl Ibotenic acid 2.5 µg/µl in one hemisphere, and 1 µl vehicle in the contralateral. After 14 days post-injection, the rats were scanned in a Bruker 7T MRI scanner using a dw-MRI sequence to extract the imaging biomarkers defined in [5] and immediately perfused for ex-vivo quantitative immunohistological analysis of microglia, astrocytes, and neurons.

As expected, neuronal staining (NeuN+ cells) was strongly reduced in the ibotenic injected hippocampus ($P<0.001$). Concomitant with the neurodegeneration, we found a strong microglia reaction (Iba1+ cells) characterized by retraction and dispersion reduction of cell processes ($P<0.0001$; $P<0.05$, respectively), together with an increase in cell density ($P<0.0001$). Notably, distinct water diffusion in the different compartments of the developed microstructural tissue model was able to detect and quantify all aspects of the microglial reaction (increased density; $P<0.05$ and decreased processes number; $P<0.001$ and dispersion; $P<0.01$) regardless of neuronal degeneration and identified a neurodegeneration fingerprint when it occurred.

This framework has the potential to disentangle glial activation with and without neurodegeneration and holds great promise to become a sensitive and specific non-invasive tool for characterizing neuroinflammation longitudinally and non-invasively.

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PS4-89

Transcranial static magnetic stimulation over visual cortex of healthy subjects

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Non-invasive brain stimulation (NIBS) techniques have been used for more than a decade to treat various diseases by the modulation of electrical activity in the cerebral cortex. NIBS could employ electrical stimulation or electromagnetic fields, such as static magnetic stimulation (tSMS). Recently, several studies have been reported that the application of tSMS on different cortical areas modulates its excitability and generally causes inhibitory effects on neuronal activity.
Our experimental hypothesis is that tSMS application over visual cortex (VCx) changes neuronal excitability in this area. For the evaluation of tSMS effects, we obtained the threshold for the generation of phosphenes by single pulses of transcranial magnetic stimulation (TMS) which has been largely employed as a measure of VCx excitability.

Twelve healthy volunteers participated in this study (eight females; mean and SD age 36.8 ± 10.6 years, range 22-57 years), recruited by local advertisement. Experiments were carried out in a real-sham, double-blinded randomized crossover study. The intervention was tSMS (or sham) applied over the occipital cortex (centered over the Oz position of the EEG 10-20 system). Intervention was performed by using a magnet (strength 120-200 mT at 2-3 cm from the scalp) or non-magnetic cylinder for sham intervention. The effect of the tSMS intervention (real vs. sham) was tested in two experimental sessions. In each session, subjects were seated in a chair in a dark room and blindfolded, and they were habituated to darkness for at least ten minutes. We assessed VCx excitability by single-pulses of TMS (≤ 0.1 Hz, circular coil) over VCx to calculate the intensity threshold for phosphenes generation. Phosphenes threshold was calculated before and immediately after tSMS intervention (or sham).
Subjects were not able to identify any difference between the magnet and sham sessions. No effects were found in the intensity threshold for phosphenes production after 10min tSMS.

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PS4-90

Immunoselective nanopheresis of Aβ in cerebrospinal fluid as a treatment for Alzheimer's disease

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Beta amyloid peptide (Aβ) is one of the main promoters of Alzheimer's disease. Originally, this protein is soluble, but it tends to self-aggregate, forming increasingly complex and insoluble structures that give rise to the characteristic senile extracellular plaques. Thus, Aβ is one of the main therapeutic targets, though none of the tried treatments to date has been effective.
Soluble Aβ is in constant equilibrium between the cerebrospinal fluid (CSF) and the interstitial fluid (ISF) in the brain parenchyma. We have previously proposed a new therapeutic strategy based on the removal of Aβ from the CSF, displacing the equilibrium, and decreasing the Aβ concentration in the brain parenchyma. To achieve this, we have designed tailored nanomembranes for Aβ nanopheresis. In this study, we evaluated nanomembranes permeability to Aβ and their impermeability to specific therapeutic agents against Aβ, such as anti- Aβ antibodies, albumin and neprilysin.
To this end, the nanomembranes were attached to a permeation chamber separating two cells: a donor cell, containing either the diffusible Aβ or the therapeutic agent dissolved in artificial CSF (aCSF), and an acceptor cell, containing only aCSF. The system was left for a maximum period of 72 hours and the levels of Aβ, and therapeutic agents were determined by ELISA. Our results showed that Aβ peptide diffuses through the nanomembrane, from the donor to the acceptor cell, whereas none of the therapeutic agents appeared in the acceptor cells. These observations support the use of nanomembranes for Aβ nanopheresis in the CSF, thus avoiding the side effects described for therapeutic agents when delivered systemically.

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PS4-91

Adjusting and validating a procedure for parenteral anaesthesia in neonatal mice

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In rodents, parenteral anaesthesia is only approved for pups over 7 days of age. By contrast, for neonatal pups only hypothermia and gas anaesthesia (halothane or isofluorane) can be used, as parenteral agents are said to cause high mortality rates. However, for experiments requiring long-term anaesthesia and a certain kind of interactions with the pups, the use of parenteral anaesthesia becomes necessary.
Here we aim at modifying the parenteral anaesthesia doses and procedures approved for pups >7 days , to anaesthetize pups for a long period with reduced mortality rates. The experiment was performed on postnatal day-3 (P3) and P4 pups and the anaesthetic doses used were 37.5 mg/kg+3.75 mg/kg ketamine+xylazine and 50 mg/kg+5 mg/kg. These doses are lower than the ones employed for >P7 pups, thus ensuring reduced mortality.
Anaesthetic was injected intraperitoneally, pups were placed in a box maintained at 37ºC, and their behaviour was video-recorded for 70 minutes. We measured the latency to absolute immobility, the latency to the first movement and the latency of awakening (continuous movement). For those pups not moving at the end of the experiment, we applied pressure to the paw and registered if they responded (yes/no). Pups were then returned to their nest and their survival was checked the next morning.
The results show that both anaesthetic doses are optimal for P3 and P4 pups, ensuring as much as 3000-to-3500 seconds of complete immobility for 50% of the pups. As expected, the latency of complete immobility shows significant, negative correlation with the duration of anaesthesia. In addition, the latency of awakening is similar in P4 pups independently of the dose, but differs significantly between doses in P3 pups. This indicates that younger pups are more sensitive to the dose of anaesthetics. Mortality is low (6%) and does not depend on the dose or age.
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PS4-92

IMPROVING THE EFFICIENCY OF HUMAN BRAIN ORGANOID GENERATION FROM PLURIPOTENT STEM CELLS

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Brain organoids were first generated by Lancaster et al. following a protocol which set the basis for human brain organoid generation. Since then, other groups have made modifications over this protocol in order to improve the organoids features or to get specific brain regions. Pașca et al. developed a protocol to get a cortex-like phenotype. They used SB-431542, an inhibitor of Transforming Growth Factor-β (TGF-β); and Noggin, an antagonizer of bone morphogenetic protein (BMP) in order to double-inhibit the TGF-β pathway and achieve a rapid neural induction. Later, other key factors have been described: Ascorbic Acid (AA) to prevent oxidation and CHIR99021, a Glycogen Synthase Kinase3β (GSK3β) inhibitor, which activates WNT signaling and promotes neural induction and neuroepithelial proliferation. We wonder whether the combination of these factors could improve and accelerate the neuroepithelium formation in order to get a more efficient and reproducible protocol. The organoids were generated from a human Embryonic Stem Cell (hESC) line, AND-2. We obtained a rapid neural induction, avoiding the Embryoid Body stage, which resulted in a direct and efficient neuroepithelium formation. With this purpose, we performed IHC and Q-RT-PCR assays for the typical neural precursor markers. We also quantified the number of organoids that formed this neuroepithelium and almost the 100 percent of them were positive, which means that our protocol permits to get homogenous organoids of similar sizes. We also performed IHC and Q-RT-PCR for additional neuronal markers at later stages and we obtained the typical Ventricular Zones (VZs) with the characteristic radial structure. All these results show that our protocol improves the efficiency and reproducibility of the traditional protocols used so far and simplifies the tedious and costly methodology that have been developed until now.

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PS4-93

In vivo and in vitro studies reveal a sex-dependent role for the insulin degrading enzyme (IDE) in memory tasks and in microglial cells

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The insulin-degrading enzyme (IDE) is a metalloprotease highly expressed at major sites of insulin degradation, but surprisingly also markedly expressed in the brain. IDE has been described to cleave not only insulin but also amyloid beta (Aß) peptides, which makes this enzyme a good candidate acting as a pathophysiological link between Alzheimer's disease and Type 2 diabetes.

To address the role of IDE in vivo we performed a comprehensive analysis of metabolic, behavioral and molecular parameters on a cohort of 12-month-old wild-type, heterozygous and knockout mice for the Ide gene. The open field test indicated that the partial or total absence of IDE does not produce significant abnormalities in the behavior of mice, while memory tests revealed sex- and genotype-dependent differences. We are currently performing a histological analysis to assess gliosis in the hippocampi of these mice and a multivariable analysis integrating all variables measured to construct a model that accounts for differences between genotypes. We then moved to in vitro studies to decipher the role of IDE specifically in primary microglial cells, master regulators of the neuroinflammatory response associated with brain degeneration and the main Aß-degrading cells. IDE absence significantly decreased microglial proliferation and delayed its response to the mitogen M-CSF. Cytokine production by Luminex assay revealed that IDE-KO microglial cells have impaired polarization under both pro-/anti-inflammatory stimuli, are more sensitive to oxidative stress, and exhibit a sex-specific pro-inflammatory response to Aß oligomers. Regarding Aß managing, amyloid phagocytosis was unchanged, but Aß degradation was diminished in IDE-KO microglia.

Our results indicate that IDE plays significant sex-dependent roles in memory tasks, and in microglial cells. IDE shows prominent functions in inflammatory polarization, microglial proliferation and Aß oligomers degradation, which makes IDE a potential therapeutic target for neurodegenerative processes.

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PS4-94

Apolipoprotein D function in microglial responses to oxidative stress and amyloid beta-triggered damage

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The brain is surveyed by microglia, resident phagocytes that show complex phenotypes. Microglia degrade injury-related cell debris, and their secreted factors modulate the immune response and tissue repair. Apolipoprotein D (ApoD) is secreted by astrocytes and myelinating glia upon injury, altered proteostasis or oxidative stress (OS). ApoD helps to maintain lysosomal functional integrity, contributes to cell survival, and optimizes macrophage phagocytosis.

Microglial cells do not express ApoD, neither in homeostatic conditions nor upon experimental OS. By adding exogenously ApoD, we found that it rapidly internalizes into BV2 microglial cells and exerts a pro-survival effect upon acute challenges of OS or β-amyloid oligomers. Following internalization, ApoD locates in vesicular cell compartments. We found a partial colocalization of ApoD with the lysosomal/endosomal marker Lamp-2, prompting further investigations on the protein traffic within microglial cells and its function in phagocytosis. We evaluated the phagocytic activity of BV2 cells upon exposure to myelin purified from wild type and ApoD-KO mouse brains. The presence of ApoD in phagocytosed myelin, or pre-exposure of microglia to exogenous ApoD, conditions phagocytosis efficiency and rate of myelin degradation, which was quantified by immunofluorescence, flow cytometry and immunoblot. ApoD influences the process in different ways depending on whether the cell is already “primed” with internalized ApoD, or ApoD enters the cell associated to the phagocytosed myelin. Multiplex analysis of cytokine production by primary microglial cells reveals that ApoD stimulates TNFα response to OS and Aβ oligomers, but not to LPS. Modulation of IL-4 production is stimulus- and sex-dependent. ApoD inhibits IL-4 secretion by male microglia in control and OS situation, but not upon Aβ exposure, while it has no influence on IL-4 secretion by female microglia. Understanding how ApoD acts on microglia, modulating its polarization and phagocytic activity upon disease-related stimuli is key to assess its neuroprotective potential.

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THE NEUROPROTECTIVE LIPOCALIN APOLIPOPROTEIN D INTERACTS WITH SPECIFIC SUBTYPES OF DETERGENT-RESISTANT MEMBRANE DOMAINS IN A BASIGIN-INDEPENDENT MANNER

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Repair mechanisms of cell membranes are critical for maintaining their roles as selective barriers and for an efficient communication and transduction of biological messages between and within cells. Plasma and lysosomal membranes contain specialized detergent-resistant domains (DRMs) rich in sphingomyelin, cholesterol and gangliosides. Maintenance of these membranes is of special relevance for the nervous system, where most neurons are long-lived cells, with a membrane-centered physiological role, and continuously challenged by oxidative stress and toxic catabolites.

The Lipocalin Apolipoprotein D (ApoD) is expressed by glial cells, secreted to the extracellular milieu, internalized by glia and neuronal cells, and targeted in a finely controlled way to the subset of lysosomes most sensitive to oxidative stress.

In this work we use membrane and isolated DRM preparations from whole brain, primary astrocytes, and glial and neuronal cell lines. Binding of purified ApoD to membranes of non-expressing neurons in vitro and ApoD detection in DRMs allow us to assay biochemical parameters on which ApoD-membrane interactions depends. We use fluorescence immunocytochemistry and confocal microscopy to test protein subcellular localization and the MTT assay to quantify cell viability.

We demonstrate that ApoD is stably associated to a particular subset of DRMs with specific buoyancy properties, co-fractionating with both plasma and lysosomal membrane markers. The association of ApoD with isolated neuronal and glial membranes is stable under metabolic and acute oxidative stress conditions. We have tested if Basigin (Bsg), a transmembrane glycoprotein reported to be an ApoD receptor, is required for ApoD-membrane association and endocytosis-dependent uptake. Using a Bsg-KO astrocytic cell line, we conclude that neither ApoD interaction with DRMs, nor its internalization, are dependent on Bsg in astroglial cells. Our current analysis centers on the dependency of membrane lipid composition, since the molecular nature of ApoD-membrane interaction is an important issue to fully understand its neuroprotective mechanism.