Neurogune

2nd BASQUE NEUROSCIENCE MEETING 2014

JULY 9th, 2014

DONOSTIA – SAN SEBASTIÁN

BASQUE COUNTRY, SPAIN

Organised by:

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PROGRAM SUMMARY

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WELCOME

Welcome to Neurogune 2014 - the second meeting of the BASQUE RESEARCH COMMUNITY IN NEUROSCIENCE

NEUROGUNE is aimed at bringing together researchers working in the Basque country who are interested in the multidisciplinary field of neuroscience, from basic research to applied clinical perspectives.

Across one day, NEUROGUNE will feature an invited speaker, 12 oral presentations covering different areas of neuroscience and 70 posters. This excellent program will cover a wide range of perspectives and subfields of neuroscience with the aim of promoting cross talk between them and specially establishing links between basic and clinical research. The one-day format and the small size of the meeting will encourage interactions among attendees.

Coupled with the aim of generating new ideas to advance the field of neuroscience from theoretical perspectives and different methodologies, the ultimate goal of Neurogune is to highlight innovative thinking that could play an important role in clinical practice and education.

We would like to express our deep gratitude to the people involved in the organization of NEUROGUNE: Miguel Arocena, Leire Arietaleanizbeascoa, Maider Goñi, Maria Domercq and Jaime Sagarduy. In addition we would also like to thank the members of the scientific committee, the research assistants, master and PhD students who will be helping during the meeting and who are a very important part of running this conference.

We hope that this second edition of the workshop in San Sebastian will be followed by a long series of NEUROGUNE meetings across the Basque Country, and that you will greatly enjoy the conference and your stay in the beautiful Donostia-San Sebastián.

Manuel Carreiras and Mari Cruz Rodriguez Oroz
On behalf of the NEUROGUNE organizing committee

WELCOME

ORGANIZING COMMITTEE

Manuel Carreiras, Mari Cruz Rodriguez Oroz, Miguel Arocena, Maria Domercq, and Jaime Sagarduy

SCIENTIFIC COMMITTEE

Manuel Carreiras, Mari Cruz Rodríguez-Oroz, Adolfo López de Munáin, Gurutz Linazasoro Cristóbal, Rosario Sánchez Pernaute, Carlos Matute, Amanda Sierra, Ugo Mayor, Abraham Martín and Joaquín Fuentes.

ACKNOWLEDGEMENTS

- We wish to thank the following sponsor for their support:
    - The Basque Government

- We would like to thank all the researchers that have submitted their abstracts to the conference.

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(PS-2.22) Does lifelong bilingualism alter the structure and connectivity of the brain?. Lorna García-Péntón, Jon Andoni Duñabeitia, Alejandro Pérez, Yuriem Fernández & Manuel Carreiras.

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ABSTRACTS

[K-1]

Exploring the synaptome: promising new technologies

Javier de Felipe

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The principal goal in neuroanatomy is to define the detailed structural design of the nervous system. This challenge is one of the first steps towards understanding how neural circuits contribute to the functional organization of the nervous system, both in health and disease. The main difficulties involve unraveling the extraordinary complexity of the nervous system and to define how information flows through this finely organized synaptic network. Over the years, neuroanatomy has evolved considerably thanks to the use of classical techniques and the introduction of new procedures. The “connectome” has recently been proposed to refer to the highly organized connection matrix of the human brain, in analogy to the human genome. However, defining how information flows through such a complex system represents so difficult a task that it would seem unlikely it could be achieved in the near future, or, for the most pessimistic, perhaps never. Circuit diagrams of the nervous system can be considered at different levels, although they are surely impossible to complete at the synaptic level. Even for a small mammal like the mouse it is impossible to fully reconstruct the brain at this level (we would need over 1.4 x 109 sections to fully reconstruct just one mm3 of tissue). Therefore, complete reconstructions of a small region of the mammalian brain are feasible, while structures like the cerebral cortex cannot be fully reconstructed. Despite the technical difficulties, by adopting appropriate strategies with the tools now available coupled with the development of huge international projects, it should be possible to make spectacular advances in unraveling brain organization, even in humans. Indeed, advances in our capacity to marry macro- and microscopic data may help establish a realistic statistical model that could describe connectivity at the ultrastructural level, the “synaptome”, giving us cause for optimism.

[OS-1.1]

Neural specialization for native speech processing in young Basque-Spanish monolingual and bilingual infants

Molnar M. [1], Quiñones I. [1], Baart M. [1], Caballero-Gaudes C. [1], Peña M. [2] & Carreiras M. [1, 3, 4]

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By 4 months of age, both monolingual and bilingual infants learn a great amount of information about their native language(s). Behavioral experiments have suggested that even though bilingual infants recognize both of their inputs as familiar and are able to discriminate them already at birth, they attend to their native languages differently as compared to their monolingual peers by 4 months of age. It is unclear why young bilingual and monolingual infants exhibit dissimilar behaviors when attending to their native languages. To assess whether exposure to two vs. one language from birth alters the neural mechanisms of native speech processing, we used near-infrared spectroscopy for recording brain activation during the presentation of native speech, native backward speech, and silence in 4-month-old Basque-Spanish monolingual and bilingual infants. Monolingual infants demonstrated clear left-lateralized responses to native speech in comparison to non-native speech, backward stimuli, or silence. Bilingual infants, however, exhibited no left-lateralized processing in either of their native languages, but demonstrated different processing of Basque and Spanish as compared to the baseline conditions. The development of neural specialization for native speech processing, therefore, appears to follow different patterns in young monolingual and bilingual infants.

[OS-1.2]

Identified risk factors for early neuropsychological development at the INMA PROJECT

Ibarluzea J. [1, 2, 3], *Santa Marina L.* [1, 2, 3], *Basterrechea M.* [1, 2], *Lertxundi A.* [2, 4], *Lertxundi N.* [2, 5], *Fano E.* [2, 5], *Vegas O.* [2, 5], *Amiano P.* [1, 2, 3], *Arranz-Freijo E. B.* [2, 5] & *Martínez M. D.* [2, 6]

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[2] BIODONOSTIA
[3] CIBERESP: Grupo 28
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[6] Consejería de Medio Ambiente

The INMA (INfancia y Medio Ambiente [Environment and Childhood]) project, aims to study the impact of environmental risk factors, both for physical and neuropsychological development. Our results are based on a prospective epidemiological birth-cohort study, with a longitudinal mother-child dyads monitoring: At pregnancy, birth and the first, second and fourth year of life. The project is composed by seven cohorts: Menorca, Flix (Tarragona), Granada, Valencia, Sabadell, Asturias and Gipuzkoa, sharing tools and study methodology.

Identified risk factors for neuropsychological development and specifically for cognitive and/or psychomotor development, assessed with the Bayley Scales (at age 1) and McCarthy Scales (at age 4), are as follows: a) iodine supplementation in pregnancy ?150 mg/day, b) exposure to organohalogen compounds (DDE , HCB , lindane, Mirex and PCBs), c) exposition to polybrominated-diphenyl ethers and perfluorinated compounds, d) exposure to Hg (methyl-Hg) and Pb, e) air pollutants, both indoor (passive smoking, gas cooking, NO2) and outdoor (PM2.5, NO2). As well as results of ongoing researches such as; cognitive development and endocrine disruptors, the poor urban environment effect and those related to maternal diet during pregnancy: low levels of antioxidants and Vitamin D, or mothers obesity effect will also be presented. The gene-environment interactions may increase the mentioned risks factors (GSTP1 polymorphisms).

[OS-1.3]

Quitting cannabis during manic or mixed episode, improve clinical and functional outcomes?

Zorrilla I. [1, 2], Nuñez N. [1], Barbeito S. [1, 2], Lopez-Peña M. P. [1, 2], Perez P. [1], Lopez S. [1], Haro J. M. [3], Gaviña J. [1], Garcia-Alocen A. [1] & González-Pinto A. M. [1, 2, 4]

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Objective: To examine whether bipolar disorder's patients who stop using cannabis during manic/mixed episode have better clinical and functional outcomes than who continue using or have never used.

Methods: EMBLEM was a 2-year prospective observational study of bipolar disorder adults with manic/mixed episode. Data was collected at baseline, during first 12 weeks of treatment, and up to 24 months. Patients were classified into three cannabis use groups: current use; no current but previous use; and never users. Cannabis effects on outcomes were analyzed using regression models.

Results: 1,922 patients were analyzed 6.9% were current users, 4.6% previous, and 88.5% never users. Clinical outcomes differed significantly between the groups (P<.019): Group stopped using had highest remission (68.1%) and recovery (38.7%) lowest recurrence rates (42.1%) and relapses (29.8%). Logistic regression showed those who stopped using had similar clinical and functional outcomes to never users (all P>.05), whereas current users had lower recovery rates (P=.0035) and remission (P=.0138), higher recurrence (P=.0138), greater work impairment (P=.0156), and were more likely not to be living with partner (P=.0055) than never users.

Conclusions: Bipolar patients who stop using cannabis during manic/mixed episode have similar clinical and functional outcomes to never users, while continue using have higher risk of recurrence and poorer functioning.

[OS-1.4]

PTEN Mediates Alzheimer's Synaptic and Cognitive Failure

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Dyshomeostasis of amyloid-ß peptide (Aß) is responsible for synaptic malfunctionsleading to a range of cognitive deficits from mild impairment to full-blown dementia in Alzheimer's disease.Aß appears to skew synaptic plasticity events towards depression. We show that inhibition of PTEN, a lipid phosphatase essential to long-term depression,rescues normalsynaptic function and cognition incellular and animal models of Alzheimer's disease. Conversely, transgenic mice that overexpress PTEN display synaptic depression that mimics and occludes Aß-induced depression. Mechanistically, Aß triggers a PDZ-dependent recruitment of PTEN into the post-synaptic compartment. Using a PTEN knock-in mouse lacking PTEN-PDZ interactions, we demonstrate that this mechanism is crucial for Aß's synaptic toxicity. Finally, we developed a pharmacological tool from the PDZ motif of PTEN that protectsneurons against Aß. These results provide fundamental information on the molecular mechanisms of Aß-induced synaptic malfunction, and may offer new mechanism-based therapeutic approaches to counteract downstream Aß signaling.

[OS-2.1]

Neuronal hyperactivity uncouples microglial phagocytosis and leads to delayed self-clearance and inflammation

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Phagocytosis is a highly conserved process essential to maintain tissue homeostasis, however little is known about its dynamics in the adult brain. Using as a model the adult neurogenic cascade, in which the majority of the newborn cells undergo apoptosis, we have established a series of parameters to quantify microglial phagocytosis dynamics. In physiological conditions, the apoptotic newborn cells are rapidly and efficiently phagocytosed by microglia. When subjected to phagocytic challenge in vivo (LPS-induced inflammation) or in organotypic slices (NMDA-induced excitotoxicity), microglia stand up to the increased apoptosis by raising proportionally their phagocytic capacity - hence, phagocytosis remains coupled to apoptosis. In contrast, microglial phagocytosis is strongly uncoupled from apoptosis in an in vivo model of epilepsy induced by kainate administration, leading to the accumulation of apoptotic cells and the development of an inflammatory response, providing the first in vivo evidence that phagocytosis and inflammation are inversely regulated. On the contrary, a lower dose of kainate induces interictal activity without inflammation and phagocytosis remains coupled to apoptosis. Therefore, our data shows that there is a neuronal hyperactivity threshold that has to be surpassed to trigger the phagocytic impairment. In fact, we provide evidence that microglia express low levels of glutamate receptors, which can mediate the microglial sensing of the surrounding neuronal activity. The mechanisms and consequences of phagocytosis blockade will be discussed.

[OS-2.2]

Adenosine A1 Receptor Inhibits Neurogenesis But Sustains Astrogliogenesis in Multipotent Neural Cells from Post-Natal Subventricular Zone

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Excitotoxic concentration of extracellular purines is among the factors inhibiting adult neurogenesis during neurodegenerative diseases. We previously demonstrated extracellular ATP released during ischemia inhibited adult neurogenesis from subventricular zone (SVZ) through the activation of specific P2X receptors. Here we wanted to study the effect of adenosine, the natural product of ATP hydrolysis, in modulating neurogenesis from the SVZ. We demonstrated by immunofluorescence and citofluorimetry that high concentration of adenosine reduces neuronal differentiation of neurospheres cultures generated from postnatal SVZ. All the adenosine receptors (A1, A2a, A2b and A3) are expressed in this cells but only A1 is involved in the inhibition of neuronal differentiation, as demonstrated by qRT-PCR, Western blot and specific gene silencing, through downregulation of a multitude of genes related with neurogenesis. We found that the mechanism by which adenosine inhibits neuronal differentiation involves the release of IL10 and further activation of the Bmp2/SMAD3 pathway sustaining indeed astrogliogenesis. In vitro data were confirmed also in in vivo neurogenesis. After intra cerebral ventricular infusion of the A1 agonist CPA we found a drastic reduction of neurogenesis and the parallel increase of astrogliogenesis in the olfactory bulb of adult rats. With this work we contribute to the knowledge of the purinergic mechanisms that regulate adult neurogenesis, especially in pathological condition when purines are released at citotoxic concentrations.

[OS-2.3]

Dopamine D4 receptor counteracts morphine-induced changes in μ opioid receptor signaling in the striosomes of the rat Caudate Putamen

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The mu opioid receptor (MOR) is critical in mediating morphine analgesia. However, prolonged exposure to morphine induces adaptive changes in this receptor leading to the development of tolerance and addiction. In the present work we have studied whether the continuous administration of morphine induces changes in MOR protein levels, its pharmacological profile, and MOR-mediated G-protein activation in the striosomal compartment of the rat CPu, by using immunohistochemistry and receptor and DAMGO-stimulated [35S]GTP?S autoradiography. MOR immunoreactivity, agonist binding density and its coupling to G proteins are up-regulated in the striosomes by continuous morphine treatment in the absence of changes in enkephalin and dynorphin mRNA levels. In addition, co-treatment of morphine with the dopamine D4 receptor (D4R) agonist PD168,077 fully counteracts these adaptive changes in MOR, in spite of the fact that continuous PD168,077 treatment increases the [3H]DAMGO Bmax values to the same degree as seen after continuous morphine treatment. Thus, even though both receptors can be coupled to Gi/0 protein, the present results give support for the existence of antagonistic functional D4R-MOR receptor-receptor interactions in the adaptive changes occurring in MOR of striosomes on continuous administration of morphine (BFU2008-02030, P09-CVI-4702).

[OS-2.4]

Modified geomagnetic fields induces C-FOS expression in encephalic neurons

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Changes in the horizontal or vertical component of the natural geomagnetic field leads to expression of c-fos in a variety of brain structures. We have investigated the role of some serin-threonin kinases such as PKCs and MEK1 on the c-fos expression after geomagnetic field application. Using individually, pharmacological inhibitors against PKCs or MEK1, we have observed that c-fos expression decreased significantly compared to the untreated animals. When we pretreated animals simultaneously with both inhibitors, the c-fos expression was dramatically decreased, meaning that PKCs cooperates with MAPkinase pathway to strongly induce this early gene expression.

Similar geomagnetic fields were applied 3 times a day during one week to visually deprived rats as a model of experimental amblyopia. A microarray study of the expression changes of c-fos promoted microRNAs in control visual cortex in comparison with amblyopic cortex revealed a lower expression of microRNAs like Rno-let-7b, Rno-miR-330 and Rno-miR-376c and consequently an increased expression of BDNF, Neurotrophin 3 and Synuclein beta, which are the main targets of these microRNAs. Absence of CpG islands in the promoter regions of the microRNAs mentioned above supress the DNA methylation as a cause of the lower microRNAs expression. In contrast, these changes, probably due to the MAPkinase pathway, were accompanied by an increase of histone acetylation in supragranular visual layers which is considered a parameter of visual recovery.

[OS-3.1]

Segmenting substructures from in vivo brain MRI using priors derived from autopsy brain samples

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Automated analysis of brain MRI at the substructure level requires computational atlases built at a higher resolution than those that are typically used in current neuroimaging studies. Here we present a method to construct a computational atlas of the hippocampal subfields and amygdaloid nuclei from heterogeneous ex vivo and in vivo MRI data.

The ex vivo data consist of autopsy samples of 16 human hippocampi and 6 amygdalae. The samples were scanned at 0.13 mm isotropic resolution (on average) using customized hardware. The hippocampal samples were manually segmented into 13 different subfields, whereas the amygdaloid samples were divided into 11 nuclei. The in vivo data consist of 39 T1-weighted MRI scans of the whole brain (1 mm resolution). These scans were manually segmented into 36 structures, and provide the computational atlas with contextual information about the hippocampus and amygdala that is (physically) not present in the ex vivo data.

The manual labels from the in vivo and ex vivo data were combined into a single statistical atlas using Bayesian inference. The atlas can be used to automatically segment the hippocampal subfields and amygdaloid nuclei in MRI scans acquired with any MRI contrast and resolution. We will show segmentation results on heterogeneous MRI data, and also present ongoing work on histology and ex vivo MRI to add the thalamus to the atlas.

[OS-3.2]

Altered SERCA expression and function in limb girdle muscular dystrophy 2A

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Limb girdle muscular dystrophy 2A (LGMD2A) is a rare neuromuscular disease affecting skeletal muscle that is caused by mutations in calpain 3 (CAPN3). This study focuses on the expression of several calcium related proteins using CAPN3 knockdown myotubes and muscle biopsies. In CAPN3 deficient human and mouse myotubes, we found significant reduction of SERCA expression and function, which resulted in impairment of calcium homeostasis. Furthermore, small Ankyrin 1 (sAnk1), a protein involved in the integrity of the sarcoplasmic reticulum network, was also reduced in CAPN3 deficient fibres. Analysis of muscle biopsies from LGMD2A patients revealed virtual absence of SERCA2 protein, whereas SERCA1 and sAnk1 were mostly reduced in patients with the lowest CAPN3 levels. Otherwise, muscle samples from patients affected by other kinds of muscular dystrophies displayed presence of SERCA2, suggesting that its absence is characteristic of LGMD2A patients. Moreover, correlation analysis of protein levels performed with 13 control and dystrophic muscle samples revealed significant positive correlations between levels of CAPN3 and those of SERCA1, SERCA2 and sAnk1. In fact, these proteins exhibited direct interaction with CAPN3, as showed by immunoprecipitation experiments in mouse skeletal muscle. In conclusion, our study supplies new evidence of the impact of CAPN3 deficiency on LGMD2A pathological development through destabilization of SERCA1, SERCA2 and sAnk1, which, in turn, compromises calcium homeostasis and sarcoplasmic reticulum stability.

[OS-3.3]

A switch from canonical to noncanonical Wnt signaling mediates early differentiation of human neural stem cells

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Wnt/beta-catenin signaling is implicated in the regulation of neural stem cell proliferation and differentiation but less is known about beta-catenin-independent Wnt signals. We show here that Wnt/AP-1 signaling, rather than Wnt/beta-catenin signaling, drives differentiation of hES and iPS cell-derived neural progenitor cells. Neuronal differentiation was accompanied by increased expression of Wnt genes, increased levels and/or phosphorylation of the AP-1 family proteins and AP-1-dependent transcription and reduced beta-catenin/Tcf-dependent transcription and target gene expression. Inhibition of Wnt secretion using porcupine inhibitors blocked neuronal differentiation, while activation or inhibition of Wnt/beta-catenin signaling had no effect. Recombinant Wnt-3a increased AP-1 protein levels and restored neuronal differentiation in cells treated with porcupine inhibitors. Restoration of neuronal differentiation was unaffected by inhibition of Wnt/beta-catenin signaling, but was reduced by inhibition of Jun N-terminal kinase and gene silencing of an AP-1 family member. Together, these results indicate that Wnt signals promote differentiation of hES and iPS cell-derived neural progenitor cells independently of beta-catenin, in a non canonical Wnt signalling pathway involving AP-1.

[OS-3.4]

Neurotoxicity and brain permeability of targeted polymeric nanoparticles

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Health safety is an important concern in nanoparticles development. In particular, their penetration in the central nervous system is an issue of outmost importance. Regarding this matter, blood brain barrier (BBB) in vitro models can be used as a useful tool for the study of nanoparticles brain permeability.

In this study we perform neurotoxicological studies of a polymeric nanoparticle alone or targeted with two different peptide ligands in order to enhance drug delivery to the brain. To this aim, glial cells, neurons and cerebral microvascular endothelial cells were employed. Subsequently, BBB permeability of the aforesaid nanoparticles was tested employing a BBB in vitro model composed of microvascular brain endothelial cells (bEND.3) and glial cells to verify if the peptide ligands improve the nanoparticle ability to cross the endothelial monolayer.

Brain permeability studies employing nanoparticles concentrations selected in neurotoxicological studies, revealed a differential ligand capacity to enhance nanoparticles permeability depending on the employed peptide.

[PS-1.1]

Molecular mechanisms controlling NMDA receptor trafficking

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Critical brain functions such as learning and memory rely heavily on accurate synaptic function and regulation. Glutamate receptor activity mediates synaptic transmission and its aberrant regulation is a shared hallmark of several neurological disorders. NMDA receptors (NMDARs) are glutamate-gated ion channels able to control synaptic plasticity and homeostasis by regulating calcium influx into the synapse. In cortex and hippocampus, functional NMDARs are tetramers composed of two GluN1 and two GluN2A or 2B subunits. Using a combination of molecular, pharmacological, immunocytochemical and electrophysiological approaches, we have investigated the regulation of NMDARs by casein kinase 2 (CK2). We have identified CK2-mediated phosphorylation of GluN2B (S1480) as a critical determinant for NMDAR trafficking. Specifically, this phosphorylation drives the removal of GluN2B from synapses via increased endocytosis, resulting in increased GluN2A synaptic expression. In addition, CK2-mediated phosphorylation controls the GluN2 subunit switch (from GluN2B-containing to GluN2A-containing NMDARs), which occurs during synaptic maturation and in response to activity. This evolutionally conserved process has important consequences in synaptic plasticity and intracellular signaling pathways. Finally, we have identified a new structural role for CaMKII, acting as a scaffolding protein that couples GluN2B and CK2 and regulates S1480 phosphorylation in response to activity. Collectively our data have provided new insight into the molecular mechanisms controlling NMDAR trafficking and synaptic function.

[PS-1.2]

The acute treatment with CB1 cannabinoid receptors agonists modulate the AChE activity at basal forebrain cholinergic projections

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The loss of cholinergic neurons and muscarinic receptors (MR) at the basal forebrain (B) has been reported in Alzheimer´s disease. Moreover, the administration of the MR antagonist, scopolamine (Scop), causes memory impairment in the rat. Controversial data have been reported about the role of cannabinoids in cognitive functions.

We evaluated the acute effect of WIN55,212-2 (1 mg/kg; i.p.) in the acetilcholinesterase (AChE) activity at basal forebrain cholinergic projections following the administration of Scop (2 mg/kg; i.p.) to rats. Passive avoidance test was used to evaluate learning and memory. [35S]GTP(Gamma)S autoradiography was used to measure the functional activity of MR and CB1 receptors at B projections. The different assays were correlated with each other. The obtained data showed an increase in AChE activity in the Scop group in several hippocampal areas that was reverted by the cannabinoid agonist (% Scop over control; CA1 Lmol (dorsal): 51±6, CA1 Lmol (ventral): 53 ± 14, CA1 Py (ventral): 27±7, CA2 Rad (dorsal): 20 ± 8, Mo DG: 53 ± 14, Po DG: 53 ± 14). These evidences support the existence of an interaction between cholinergic and cannabinoid systems in brain areas related to learning and memory.

[PS-1.3]

Regulation of neurogenesis by phagocytic microglia-derived factors

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During neurogenesis in the adult hippocampus, a large part of the newborn cells die by apoptosis. To prevent disturbance of surrounding neurons, apoptotic cells are quickly and effectively removed by phagocytosis by resident microglia. We hypothesize that phagocytic microglia contribute to maintaining the balance of adult hippocampal neurogenic cascade by producing neurogenic factors. To test this hypothesis, we analyzed the expression of neurogenic factors produced by cultured microglia after feeding them with apoptotic NE4C (a mouse neuroprogenitor line) or SH-Y5Y (a human neuronal line) cells. Our data shows that when given apoptotic NE4C cells, 90% of microglia were already phagocytosing within the first hour. Otherwise, for the SH-Y5Y cells, microglia could not reach this percentage until 15 hours, probably due to the need of unconventional recognition mechanisms to phagocytose human apoptotic cells. Moreover, we analyzed different factors secreted by microglia during the assay and found that all of them underwent changes in their expression pattern. To account for possible differences between postnatal and adult microglia, as well as in vivo and in vitro, results were also validated in FACS-purified microglia from dentate gyrus of the adult hippocampus (1-month-old), where apoptosis and phagocytosis are abundant, and CA and cortex, where apoptosis or phagocytosis barely occurs. In conclusion, this could be the first step to elucidate whether the neurogenic cascade is regulated by microglia.

[PS-1.4]

Reactive Neural Stem Cells in Response to Injury in the Hippocampus

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Radial neural stem cells (rNSCs) persist in the hippocampus of most mammals and are able to generate neurons through adulthood, a process known as adult neurogenesis. Adult hippocampal neurogenesis is important for spatial memory, pattern separation and the responses to fear, stress and anxiety. rNSCs are mostly quiescent but once they are activated, they generate neuronal precursors through several rounds of asymmetric division and then differentiate into astrocytes, losing their stem cell capabilities. We have recently discovered that after seizures rNSCs become reactive, entering symmetric division and differentiating into reactive astrocytes at the expense of their neurogenic potential.

We now hypothesize that this reaction can be a common response of rNSCs to injury. Using a model of stab wound targeting the dentate gyrus, we have found that rNSCs also become reactive and convert into reactive astrocytes in a similar manner to the situation observed after seizures. We are now exploring the long-term consequences for the neurogenic niche of rNSCs becoming reactive in this injury model. Using transgenic mice in which rNSCs can be visualized, we are investigating whether the rNSC population becomes depleted and as a consequence neurogenesis becomes chronically impaired. The loss of neurogenesis might be detrimental at two levels: impairment of the specific functions related to this process and the impossibility to regenerate the neuronal loss induced by the injury.

[PS-1.5]

Functional, structural and metabolic remodeling related to cognitive recovery in ischemic stroke patients

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The main aim of the current PhD research was to identify functional, structural and metabolic changes of patients suffering from an ischemic stroke and to attempt to relate them with cognitive recovery by applying the most up-to-date neuroimaging techniques.

Much of our current knowledge in relation to cognitive brain function is based on the modular paradigm, in which brain areas are postulated to act as independent processors for specific complex cognitive function. This paradigm, although has helped to build much of the present understanding of disease pathophysiology, has serious limitations when applied to the explanation of clinical and cognitive dysfunctions after a neurological insult. In stroke, clinical and cognitive deficits are not always easily explicable by the lesion localization itself, lesions of some areas tend to have more severed effects than others and individual outcomes seem to be due more to residual anatomy than to lesion localization. This scenario makes difficult to predict which patient will recover and will reintegrate into society and which will be relegated to a life of disability.

Novel research utilizing probabilistic Independent Component Analysis, Diffusion Tensor Imaging, Spectroscopy Imaging, and Graph Theory Analysis has reported properties of the human brain as a complex network as well as has revealed that the contralesional hemisphere is not so ?healthy? as assumed at first glance.

[PS-1.6]

The Neurogenic Niche of Human Hippocampus in Mesial Temporal Lobe Epilepsy

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Mesial Temporal Lobe Epilepsy (MTLE), the most common form of drug-resistant epilepsy, affects the hippocampus and related limbic structures. MTLE is characterized by recurrent focal seizures and the development of hippocampal sclerosis. Typical landmarks of hippocampal sclerosis are neuronal death and dispersion; and gliosis with massive presence of reactive astrocytes. The hippocampus is one of the two areas where neurogenesis, the formation of new neurons, takes place in the adult brain. Hippocampal neurogenesis is important for spatial memory and learning; pattern separation; and the responses to fear, anxiety and stress and pattern association memory. The effect of seizures on hippocampal neurogenesis has been studied but opposite results has been reported.

Working with mice and an experimental model of MTLE we have determined that neurogenesis is impaired in the long term. Impaired neurogenesis might have two detrimental effects: a loss of the functions associated with neurogenesis, and a loss of the restorative potential of neural stem cells. We are currently analyzing human hippocampi from MTLE patients and our preliminary results show, in agreement with our findings in mice, that putative neural stem cells, cell proliferation and newborn neurons are absent in the epileptic human hippocampus. We hypothesize that impairment of neurogenesis might contribute to the cognitive deficits and psychiatric comorbidities associated with MTLE in humans.

[PS-1.7]

Effect of buspirone on the subthalamic nucleus on an animal model of parkinson's disease: An electrophysiological study

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The most effective treatment for Parkinson's disease (PD), L-DOPA, induces dyskinesia (LID) after prolonged use. We have previously shown that in 6-hydroxydopamine lesioned rats rendered dyskinetic by prolonged L-DOPA administration, lesion of the subthalamic nucleus (STN) reduces LID and buspirone antidyskinetic effect. This study examined the effect of buspirone on STN neuron activity. Single-unit extracellular recordings were performed in vivo on STN neurons from four different groups, i.e., control, chronically treated with L-DOPA, lesioned and lesioned chronically treated with L-DOPA (dyskinetic) rats and in vitro cell-attached recordings. In control rats buspirone administration decreased the firing rate in a dose-dependent manner. This effect was absent in 6-OHDA lesioned rats and was not modified by acute or prolonged L-DOPA administration. In addition, in control rats the 5HT1A antagonist WAY-100635 and the D3 antagonist PD128907 prevented the effect of buspirone. Conversely, in parasagittal slices containing the STN, buspirone induced excitatory, inhibitory and also biphasic responses being only the inhibitory effect prevented by WAY-100635. Buspirone in vivo reduces the firing rate of the STN neurons through 5HT1A and D3 receptors whereas in vitro buspirone seams to show a more variable effect. Moreover, buspirone lack of effect in 6-OHDA lesioned rats, suggests that the STN may not be directly involved in its antidyskinetic effect.

[PS-1.8]

Retinal ganglion cell axons regrow despite persistent astrogliosis in the lizard

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We analysed the astroglia response that is concurrent with spontaneous axonal regrowth after optic nerve (ON) transection in the lizard Gallotia galloti. At different post-lesional time points (0.5 to 12 months), we used conventional electron microscopy and specific markers for astrocytes (GFAP, vimentin (Vim), Sox9, Pax2) and for proliferating cells (PCNA). In the experimental retina the increase of gliofilaments was not significant and proliferating cells were undetectable. Conversely, PCNA+/GFAP+ and PCNA+/Vim+ reactive astrocytes were identified in the regenerating ON and optic tract (OTr). They up-regulated Vim at 1 month post-lesion, and both Vim and GFAP at 12 months post-lesion, indicating long-term astrogliosis. They also expressed Pax2, Sox9 in the ON, and Sox9 in the OTr. Concomitantly, persistent tissue cavities and disorganised regrowing fibre bundles reaching the OT were observed. Our ultrastructural data confirm abundant gliofilaments in reactive astrocytes joined by desmosomes. Remarkably, they also accumulated myelin debris and lipid droplets until late stages, indicating their participation in myelin removal. These data suggest that persistent mammalian-like astrogliosis in the adult lizard ON contributes to a permissive structural scaffold for long-term axonal regeneration and provides a useful model to study the molecular mechanisms involved in these beneficial neuron-glia interactions. This work was supported by the Spanish Ministry of Education (Research Project BFU2007-67139), the Regional Canary Island Government (ACIISI, Research Projects SolSub200801000281 and ULPAPD-08/012-4).

[PS-1.9]

P2X4 receptors modulates microglial polarization

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Microglial activation is an integral part of neuroinflammation contributing to neurological damage in experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS). We have previously shown that P2X4 receptor is overexpressed in activated microglia in the spinal cord of EAE rats and in human MS optic nerve samples. Because microglial polarization to an M2 phenotype favors remyelination in the EAE model (Miron et al., 2014), we have analyzed the role played by P2X4 receptor in microglial polarization. The blockage of P2X4 receptors in cultured microglia favors M1 differentiation and significantly inhibits M2 polarization. Factors controlling microglial polarization, like macrophage granulocyte colony stimulating factor (MG-CSF; M1-inducing factor) and macrophage colony stimulating factor (M-CSF; M2-inducing factor), also induces multinucleated giant cell formation. Surprisingly, P2X4 receptor blockage exclusively antagonized M-CSF induced multinucleation, suggesting a possible interaction with CSF-1R signaling pathway. Moreover, preliminary data showed that conditioned medium from M1 and M2 microglia differentially controls oligodendrocyte development and that P2X4 receptor blockage significantly reduces M2-dependent oligodendrocyte differentiation. Accordingly, blocking P2X4R inhibits remyelination whereas potentiating P2X4R signaling favors remyelination in cerebellar organotypic cultures after lysolecithin treatment. These results suggest that microglial P2X4 receptor could be a target to promote remyelination in demyelinating diseases.

[PS-1.10]

Amyloid beta oligomers regulate oligodendrocyte differentiation and myelination

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Amyloid beta (Abeta) oligomers are key peptides involved in Alzheimer´s disease (AD) pathogenesis. The effects of these oligomers on white matter, and specifically on oligodendrocytes (OLG) are still poorly understood, even though their damage may contribute to cognitive decline in AD. Here, we have investigated the role of Abeta oligomers in OLG differentiation and myelination in vitro and in vivo. Using a panel of developmental stage-specific antigenic markers, we observed that Abeta oligomers modified the differentiation pattern, regulating the transition of early progenitors to the late progenitor stage (O4 positive cells) and to the inmature to mature OLG stage (MBP positive cells) in OLG in vitro. To further investigate the pathway underlying Abeta-mediated OLG differentiation, we analyzed the phosphorylation levels of three key proteins involved in myelin synthesis, AKT, ERK and CREB. We found that Abeta oligomers promoted a sustained AKT dephosphorylation, and ERK and CREB phosphorylation and the specific pharmacological inhibition of these pathways reduced the Abeta-induced MBP upregulation in cultured OLGs. Furthermore, Abeta oligomers increased the MBP levels in cultured cerebellar slices in control and in lysolecithin-induced demyelination conditions. This Abeta-mediated myelin upregulation was confirmed in the corpus callosum of a mouse model of AD. Our data suggest that Abeta oligomers induce OLG differentiation through MAPK/ERK, PI3K/AKT and PKA/CREB signaling pathways, which may be relevant to understand AD pathophysiology.

[PS-1.11]

Activity mediated by receptors for neurolipids, CB1 and LPA1, in a rat model of basal forebrain cholinergic lesion

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The cholinergic basal forebrain, which innervates cortical, hippocampal and amygdaloid areas, controls learning and memory processes and is damaged in Alzheimer´s disease. The present study analyzed learning and memory after the selective basal forebrain lesion with 192IgG-saporin (SAP). A significant decrease was observed in cholinergic neuron density (P75NTR-ir) in SAP treated rats (-82,7% vs aCSF, p<0,001). We found that cognitive impairment and reduction in P75NTR-ir correlated with each other (r2=0,51, p<0,05). Similar results were observed with decreasing AChE staining in cortical areas (entorhinal: r2=0,55, p<0,01), hippocampus (CA3: r2=0,49, p<0,01) and amygdala (anterior: r2=0,43, p<0,01). We also found a high CB1-ir in basal forebrain of lesioned rats. [35S]GTP-GammaS autoradiography revealed increased CB1 receptor activity stimulated by WIN55,212-2 (10 uM) in lateral olfactory tract (data expressed in % stimulation over basal; CSF vs SAP; 55 ± 11% vs 128 ± 13%, p<0.05) and in entorhinal cortex (156 ± 17% vs 277 ± 30%, p<0.01), but decreased in dentate gyrus (229 ± 32% vs 139 ± 19%, p<0.05) and in medial amygdala (116 ± 20% vs 50 ± 7%, p<0.05). Lysophosphatidic acid (LPA) (10 uM) stimulation showed an increase in the internal capsule (60 ± 10% vs 137 ± 19%, p<0.01). The modulation of CB1 and LPA1 receptor activity in response to the cholinergic impairment may indicate a neuroprotective action in basal forebrain.

[PS-1.12]

Effect of Hypoxic-ischemic event in the auditory threshold in a rat model

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Maturation of the auditory pathway is related to central nervous system myelinization and can be affected by pathologies such as neonatal hypoxic-ischemic encephalopathy. To evaluate the auditory capacity in newborns, it is commonly used the auditory evocated potentials (AEPs).

Our objective is to determinate the functional integrity of the auditory pathway and to visualize the damage in the brainstem using a model of hypoxic-ischemic (HI) brain injury in neonatal rats.

7-day-Sprague-Dawley rats were randomly assigned to the SHAM groups (no ischemic or hypoxic injury) and the HI groups (permanent left carotid occlusion and reduction of 02 to 8%) by Rice-Vannucci method. The AEPs were measured at 14 days and animals were sacrificed and the brainstem isolated, paraformaldehyde fixed, paraffin included, sectioned and stained with hypoxiprobe kit.

The Auditory Pathway was altered during the hypoxic-ischemic insult, with an increase in the latency of the I-V and III-V waves' ratio.

At histological level, the hypoxiprobe kit stained cells exposure to a reduction of the oxygen, so we observe in the HI group a different staining comparing to the SHAM. Besides, we observe a difference in the morphology of the brainstem in the left side comparing to the SHAM group owing to the ischemic event.

Our results suggest that the HI event reduces the auditory capacity and generate neuronal damage in the brainstem.

[PS-1.13]

Blockade of the 2-AG hydrolase ABHD6 ameriorates disease progression in the experimental autoimmune encephalomyelitis model of multiple sclerosis

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Preclinical and clinical research has demonstrated the utility of activating cannabinoid receptors in inflammatory diseases of the central nervous system such as multiple sclerosis (MS). Nevertheless, the therapeutic use of exogenous agonists is limited by the possible adverse responses related to memory and learning impairment. An alternative therapeutic strategy consists of enhancing the concentration of the endocannabinoids anandamide and/or 2-arachidonoylglycerol (2-AG) by decreasing their enzymatic metabolism. In this context, we have investigated the potential of targeting the recently characterized 2-AG hydrolitic enzyme ABHD6 (α/β hydrolase domain lipase 6) as novel therapeutic strategy in MS. With this aim, we have studied the effects of centrally acting and peripherally restricted ABHD6 selective inhibitors in the experimental autoimmune encephalomyelitis (EAE) model of MS. Chronic EAE was induced in C57BL/6 mice by immunization with MOG in Freund's adjuvant supplemented with Mycobacterium tuberculosis. Mice were treated daily with KT182 or KT203 (2 mg/kg) starting at the day of immunization. Comparison of the motor score curves indicated that although both ABHD6 inhibitors ameliorated the deficits observed in vehicle-treated mice during the disease course, the brain permeable compound was more effective than the peripherally acting one. The ability of both to attenuate the gene expression of proinflammatory cytokines in the brain of EAE mice is currently under investigation.

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[PS-1.14]

Resveratrol atenuates brain damage after perinatal hypoxic-ischemic injury in rats

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Perinatal asphyxia and the resultant hypoxic-ischemic encephalopathy (HIE) can be devastating, resulting in death or severe neurological consequences. Resveratrol is a polyphenol with antioxidant properties. The aim of the present work was to assess whether resveratrol plays a protective effect when administered 10 minutes before or immediately after HI brain injury in neonatal rats using the Rice-Vannucci model.

PN7 pups were exposed to an HI insult, the left common carotid artery was permanently occluded and maintained under hypoxia (8% oxygen) for 135 minutes. Animals were treated with 20 mg/kg of resveratrol 10 minutes before hypoxia (RVT before) or immediately after (RVT after). Pups without injury were used as controls. PN14 brains were stained with Nissl and immunolabelled with MBP. T-maze, hole-board and novel object recognition tests were carried out on post-natal day 90.

The brains of HI and RVT after groups showed an infarct area in the ipsilateral hemisphere, while no macroscopic differences were observed between Control and RVT before. RVT before obtain better results in neuropathological scoring. Ratio of ipsilateral-contralateral hemispheric MBP showed a significant decrease in HI group in comparison with control, that was restored when resveratrol is administered before hypoxia. On PN90, RVT before animals performed better at neurobehavioral tests.

Our results suggest that a pretreatment with resveratrol reduced infarct volume, preserved oligodendroglial viability and improved long-term behavioural impairments.

[PS-1.15]

Effect of a novel modulator of ryanodine receptor 1 in the mdx mouse model of Duchenne muscular dystrophy

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The sarcoplasmic reticulum receptor RyR1 is abnormally nitrosylated within the skeletal muscle of mdx and Sgcb-/- dystrophic mice, which results in calstabin1 depletion from the RyR macromolecular complex and a subsequent calcium leak to the cytosol. RyR1 modulators such as S107, have recently demonstrated their efficacy in vivo by ameliorating muscle damage and improving muscle function in these mice.

In this work we have studied the effect of A6, a novel RyR1 modulator designed and synthesized by our group that shows less in vitro citotoxicity than S107. During a 5-week experiment, limb strength, CK and LDH serum levels were assessed weekly in 3 groups of mice: control, non-treated mdx and A6-treated mdx. At the end of the experiment mice were sacrificed and muscles were dissected for histological analysis. We also analyzed intracellular calcium levels in isolated fibres from flexor digitorum brevis muscles of these mice. We found that in mdx isolated fibres, A6 treatment reduces significantly basal cytosolic calcium concentration to the levels observed in control fibres. Furthermore, we observed that A6 treatment reduces histological evidence of muscle damage and improves muscle function.

In conclusion, our study shows that A6 is effective in reducing cytosolic calcium levels and improving muscular function in mdx mice. In addition, it consolidates RyR1-calstabin1 interaction as a useful therapeutic target for drug development against muscular dystrophies.

[PS-1.16]

Dysfunctional inhibitory mechanisms in locus coeruleus neurons of the Wistar Kyoto rat

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The Locus coeruleus (LC) nucleus is widely implicated in depression. In addition to glutamatergic and GABAergic synaptic inputs, activation of α2-adrenoceptors mainly regulates LC activity. The goal of this study was to investigate the sensitivity of α2-adrenoceptors, as well as glutamatergic and GABAergic synaptic activity of LC neurons from the Wistar Kyoto (WKY) rat, an animal model of depression, using patch-clamp whole-cell recordings. The α2-adrenoceptors from WKY rats were less sensitive to the agonist, UK than those from Wistar control rats. Beside a shorter rise time of the sEPSC no other significant alterations were detected in glutamatergic transmission of LC neurons from WKY. However, the GABAergic input was significantly altered in WKY rats, since sIPSC displayed reduced amplitude and increased half-width. These results point out that the inhibitory control exerted by α2-adrenoceptors and GABAergic input onto LC neurons is dysregulated in WKY rats. This study highlights the mechanisms underlying altered neurotransmission in the LC of WKY rats, supporting the hypothesis that claims an unbalance between the glutamatergic-GABAergic systems as a key factor in the pathophysiology of depression.

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[PS-1.17]

Oscillatory responses to highly predictable words differentiate between expectations based on semantic or associative contextual constraints

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During language comprehension, semantic contextual information is used to generate expectations about upcoming items. This has been frequently studied through the N400 event-related potential (ERP), as a measure of facilitated lexical retrieval. However, the associative relationships in multi-word expressions (MWE) may enable the generation of categorical expectations, leading to lexical retrieval before target word onset. Processing of the upcoming word would thus involve a target-identification mechanism, possibly indexed by a P3 component. However, given their time overlap (200-500 ms post-stimulus onset), differentiating between N400/P3 ERP responses is problematic. In the present study, we analyzed EEG data from a previous experiment, which compared ERP responses to highly expected words placed either in a MWE or a regular compositional context. We focused on time-frequency and single-trial statistical analyses, in order to use individual item variability to dissociate between conditions. A significant correlation between word position and power in the theta band (7-9 Hz) was found only for MWE, providing evidence for the presence qualitative differences between conditions. Power levels within this band were lower for MWE than compositional contexts, suggesting that in the former lexical retrieval had taken place before word onset. On the contrary, gamma-power was modulated by predictability of the item in all conditions, which could reflect similar 'matching' sub-steps in the binding process between an expected representation and the external input.

[PS-1.18]

What the Ear Hears Affects What the Eyes See: Semantic Interference on Visual Task Performance

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According to sensorimotor accounts, object representations are distributed over the same brain areas that are active when experiencing those objects. Because these accounts hold that conceptual representations are experience-based, they predict that representations of objects with which we have relatively-more visual experience should involve brain areas supporting vision more than those with which we have relatively-less. One possible consequence of this account is that accessing representations of "more-visually-experienced" objects could impair performance on an incompatible visual task more than "less-visually-experienced objects" because of competition for shared resources in brain areas supporting both visual task performance and "more-visually-experienced" objects' representations. We tested this prediction in a behavioral experiment where participants performed a Multiple Object Tracking task while they made concreteness judgments about aurally presented object names which varied (according to ratings) in the relative amount of visual experience participants had of them (e.g. "pencil"= less-visual, "penguin"= more-visual). Results show that participants had greater difficulty with the MOT task when making concreteness judgments on "more-visual" objects than on "less-visual" objects. This interference suggests that: (a) the conceptual representations of frequently seen objects share resources with parts of the visual system required to perform Motion Object Tracking, (b) visual information is accessed when performing concreteness judgments on "more-visual" words, and that (c) visual task performance can be interfered with by thinking about "more-visual" objects.

[PS-1.19]

Bilingual language discrimination: Electrophysiological evidence for language selectivity

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How do bilinguals detect the language of a word that they are reading? In the current study we investigated the extent to which language detection is modulated by the sub-lexical orthographic regularities of the words. Bilinguals completed a reading task in which Spanish targets were briefly preceded by unrelated words either in Spanish or Basque (masked language switch priming paradigm) while their electrophysiological activity was recorded. The bigrams of the Basque words were manipulated as a function of their legality in Spanish (i.e., legal vs. illegal bigrams). Results showed switch cost effects in the N250 and N400 components only for Spanish words preceded by Basque primes containing Spanish-illegal bigrams, and a clear lack of such effects for Basque words whose bigrams did also exist in Spanish. A replication of this experiment with Spanish monolinguals with no knowledge of Basque showed a markedly different pattern, with significant switch cost effects in the N250 and N400 components for Spanish words preceded by Basque primes containing Spanish-illegal and Spanish-legal bigram combinations. These results demonstrate that bilingual readers process orthographically marked words differently from orthographically unmarked words and that language detection mechanisms in bilinguals are based on statistical orthographic regularities. In light of these results, we conclude that bilinguals process language-unmarked words faster than language-marked words.

[PS-1.20]

Reading minds: How and where does orthographic processing occur in the brain?

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In alphabetic languages visual word processing requires relatively precise identification of the individual letters that constitute each word and of the position occupied by each letter within the string. After decades of intensive behavioral and neuroimaging research, the specific neural circuits recruited for alphabetic coding are still unclear. While some theoretical models propose that position-in-string coding responds to general flexible mechanisms of the visual system that are character-unspecific, recent results call into question this assumption. We will review recent evidence at this regard obtained from samples of developing readers (i.e., schooled children of different ages), illiterates, and adult expert readers, demonstrating that letter position coding responds to specific processes that are different from those that guide position-in-string assignment of other types of visual objects such as digits or symbols. Besides, we will demonstrate that the emergence of letter-specific coding mechanisms is closely linked to the literacy process. Finally, we will present fMRI evidence demonstrating that clearly differentiated brain areas respond more to letters than to other alphanumeric characters and vice versa (i.e., different brain pathways engaged in the processing of different types of visual characters), and that a specific region in the left hemisphere (the left parietal cortex) is particularly involved in letter identity and position coding.

[PS-1.21]

Hippocampus dependency to in-body encoding

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We generally encode life-experiences into memory from a first-person in-body representation. But how dependent is the hippocampal long term memory system to this in-body representation? While participants were involved in a social interaction, an out-of-body illusion was elicited, in which the sense of bodily self was displaced from the real body to the other end of the testing room. This condition was compared with a well-matched in-body illusion condition, in which the sense of bodily self was colocalized with the real body. In separate recall sessions, performed ~1 wk later, we assessed the participants' episodic memory of these events. The results revealed an episodic recollection deficit for events encoded out-of-body compared with in-body. Functional magnetic resonance imaging indicated that this impairment was specifically associated with activity disturbance in the posterior hippocampus. These findings suggest that the in-body encoding is necessary for the formation of the long term memory of an event. The results thus provide the first step in the explanation for the link between the impaired episodic memory and dissociative symptoms (where a person feels detached from their own body) that occur in clinical conditions such as post-traumatic stress disorder and schizophrenia.

[PS-1.22]

Interaction between resting state networks in Alzheimer disease

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The resting brain dynamics self-organizes in a finite number of correlated patterns known as resting state networks (RSNs). Currently it is well-known that techniques like independent component analysis can separate the brain?s resting state functional magnetic resonance imaging activity to provide such RSNs but the specific pattern of interaction between these RSNs is not well understood yet. To this aim, we propose here a novel method to compute the information flow between different RSNs. Our method first uses principal component analysis to reduce dimensionality in each RSN to then compute the information flow between the different RSNs by systematically increasing k (the number of principal components used in the calculation). When k=1, this method is equivalent to computing the information flow between the average voxels activity in each RSN. For k>= 1, our method calculates the k-multivariate transfer entropy between the different RSNs. Our results are two-fold: first, the pattern of information flow was dimension dependent, increasing from k=1 (average voxels activity) up to reach a maximum at k=5 to finally decay to zero for k bigger than 10. Therefore, the total amount of transferred information does not grow monotonically with the dimension. Second, we have applied our method to compare inter-RSNs information transfer between Alzheimer patients and controls. The more significant differences in between AD and control groups occurred for k=2. This allowed us to perform a paired t-test to spatially localize the k=2 component, thereby identifying within-RSN brain regions related to differential information transfer between Alzheimer's and controls. We conclude that this methodology can unravel aspects regarding the resting state organization and dynamics of the Alzheimer disease.

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[PS-1.23]

Discrimination of auditory hallucination sensitive Schizophrenia patients from resting state functional MRI

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Abstract The application of machine learning techniques in the field of neurosciences provides to new ways to treat and extract information from neurological data. Application to neuroimage provides new insights and biomarkers that complement those found by statistical inference. This paper deals with resting state funcional Magnetic Resonance Imaging (rs-fMRI) data from Schizophrenia patients with and without a history of auditive hallucinations, and matching controls. We study the binary classification problems arising when considering the discrimination of each pair of subject categories. The steps of the computational process are as follows: (a) rs-fMRI data normalization and preprocessing, (b) reduction of the multivariate data to scalar measures, (c) feature selection, (d) feature extraction, (e) ten fold cross-validation experiments of the classifiers. This study includes the evaluation of four methods to obtain the scalar measures of the rs-fMRI data. Namely we study two functional connectivity measures based on lattice auto-associative memories, respectively. The study includes features from two measures of rs-fMRI spatial coherence and activity. We report very good classification results. We focus on the specific discrimination of Schizophrenia patients with and without auditory hallucinations, showing the brain localizations of discriminant regions for each scalar measure.

[PS-1.24]

Structural and Functional Cerebral Correlates of Memory in Parkinson Disease

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Introduction:
Neuroimaging studies have increased our understanding of Parkinson Disease (PD). The goal of this study was to combine functional magnetic resonance (fMRI) with diffusion tensor imaging (DTI) to better understand the neural mechanisms that underlie verbal memory (VM) dysfunction in PD.

Methods:
Thirty-three non-demented PD patients participated in this study. Memory was assessed with a codification fMRI paradigm. DTI and fMRI were acquired on a Philips Achieva 3T. FA values were calculated after running TBSS as implemented in FSL. Pearson´s Correlation Coefficient was used to investigate the correlation between structure and function.

Results:
Activation values while performing the memory task in left orbitofrontal inferior showed a positive correlation with FA values of callosal body (r=.365, p=.034), left (r=.353, p=.041) and right (r=.398, p=.020) inferior longitudinal fasciculus, right fronto-occipital (r=.345, p=.046), left optic radiation (r=.372, p=.030) and left (r=.448, p=.008) and right (r=.419, p=.014) corticospinal tract. Activation values in right amygdala correlated with FA of left corticospinal tract (r=.437, p=.010). There was a negative correlation between activation in right medial temporal lobe and FA of right uncinate fasciculus (r=-.417, p=.014).

Conclusions:
These results suggest that stronger activation values in several brain areas are associated with higher integrity in WM tracts. The present data represent a first step toward an integration of functional and structural MRI in the investigation of memory in PD.

[PS-1.25]

White matter differences in subtypes of Mild Cognitive Impairment in Parkinson Disease

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Introduction:
Mild cognitive impairment (MCI) is common in Parkinson´s disease (PD) but neuroanatomical description of MCI profiles is needed. The purpose of this study is to assess white matter (WM) fractional anisotropy (FA) differences in subtypes of MCI in PD.

Methods:
Thirty-three PD patients (mean age=67.64 ± 6.535) and 44 HC (age, gender and years of education-matched) underwent a neuropsychological battery and magnetic resonance imaging (DTI and T1) was acquired. Whole-brain voxel-wise and ROI analysis were performed using TBSS (Tract-Based Spacial Statistics) to assess FA. MCI diagnostic criteria were 1.5 SD below HC group.

Results:
Ten PD patients showed no_MCI, 6 showed single domain MCI (SD-MCI) and 17 multiple domain MCI (MD-MCI). Mean FA values: no_MCI group (m= .348; s.d.=.011), SD-MCI group (m=.345; s.d.= .010) and MD-MCI group (m=.336; s.d.=.012) but were not statistically different. WM FA significant differences were found between MD and no_MCI subtypes in right inferior longitudinal fasciculus (p=.020), inferior fronto-occipital fasciculus (p=.022), optic radiation (p=.010) and right (p=.025) and left (p= .026) corticospinal tract. In addition, differences were found between MD and SD-MCI subtypes in right (p=.35) and left (p=.004) corticospinal tract.

Conclusions:
WM principal tracts connecting the frontal, temporal, parietal and occipital lobe showed significant differences between MCI subtypes. These findings suggest the existence of different neuroanatomical substrates for MCI subtypes in PD.

[PS-1.26]

Investigating the dynamics of human brain function at rest with paradigm free mapping and BOLD fMRI

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A plethora of sensory and association brain areas must dynamically and coherently communicate to each other in order to integrate, process and respond to internal and external stimuli. Such functional brain networks exhibit a degree of synchronous activity that is not only fundamental to support cognition and behaviour, but also remarkably informative in the resting state (RS). Traditionally, BOLD fMRI RS functional connectivity studies have implicitly assumed a static interdependence between the signals of different brain regions. Only few works have investigated the wealth of information available in the non-stationarity of spontaneous BOLD activity, and evidenced these dynamics can reveal important aspects of brain function. For instance, functional brain networks can be distinctly mapped by considering as few as 15% critical time points of the signal (a.k.a. point process analysis (PPA)), which are then spatially clustered. However, this approach is likely to be prone to signal artefacts and non-physiological fluctuations that modulate the BOLD signal. Here, we demonstrate that paradigm free mapping, a novel analysis tool that detects single-trial BOLD events without prior timing information, can serve as a more robust method to investigate the dynamics of functional brain connectivity, avoiding ad-hoc choices of the number of critical time points and amplitude thresholds inherent to PPA. Our results further corroborate that RS functional connectivity is driven by brief spontaneous BOLD events.

[PS-1.27]

MicroRNA expression in a mouse model of retinitis pigmentosa

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Purpose: Retinitis pigmentosa (RP) is the most common form of inherited retinal degeneration associated with progressive dysfunction of rod cells and/or cones. Currently there is no standardized and effective treatment for this eye disease that affects about 1 million people worldwide. Here we propose that an alteration in the expression of microRNAs (miRs) is involved in the pathogenesis of RP.

Methods: Using PCR-based expression microarrays we analyzed the expression of miRs in retinas from an RP mouse model, with photoreceptors death related to an alteration of intracellular Ca2+.

Results: We found 3 miRs with a 5 to 15-fold decreased expression and one miR with a 44-fold increased expression.

Conclusions: Our results support the implication of miRs in RP. Overexpression of one of the altered miRs we found has been linked to increased release of Ca2+. This miR has been reported to target among other genes: PIK3CA, expressed in photoreceptors; connexin 43 and the potassium channel Kir2.1, both expressed in retinal glial cells. Interestingly overexpression of these glial components have been involved in retinal damage induced in experimental models and therefore might be also involved in the mechanism of cell death that takes place in our RP model.

[PS-1.28]

Identification of key small non-coding RNAs in the sncRNA- mRNA coexpression network alterations associated to multiple sclerosis

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It has recently been revealed that small non-coding RNAs (sncRNAs), especially microRNAs (miRNAs), may play important roles in the pathogenesis of Multiple Sclerosis. miRNAs have been shown to be central players in the postrancriptional regulation of gene expression, whose study has incorporated a powerful mathematical tool: network modelling. With the aim of identifying the alterations at the sncRNA - mRNA regulatory level related to the disease, we have constructed sncRNA - mRNA coexpression networks. In total, 65 samples (22 patients in relapse and remission and 21 healthy controls) were collected for the study. RNA was isolated from peripheral blood leucocytes and whole genome gene expression was measured for both mRNAs (Human Gene 1.0 ST array (Affymetrix)) and sncRNAs (GeneChip miRNA array v1 (Affymetrix)). Our results highlight that sncRNA-mRNA coexpression networks, in contrast to most gene expression correlation networks, present a scale-free topology. They also reveal the central role of some miRNAs and snoRNAs in the global regulation of transcriptional activity. The analysis of differential connectivity performed on the status-specific networks (the relapse, remission and controls networks) shows that the three networks are very different (the number of common edges is very low). Finally, the network centrality measures of the disease-specific network identify some sncRNAs as having a central role in that network and that would be potential candidates for therapeutic targeting.

[PS-1.29]

Retrograde axonal and neuronal degeneration of the retina in acute optic neuritis

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Objectives: to assess the dynamics of retinal damage after acute optic neuritis (ON) by Optical Coherence Tomography (OCT) and to identify early OCT predictors of visual disability to improve the understanding and clinical management of axonal and neuronal degeneration in ON.

Methods: 31 patients with ON (idiopathic or Multiple Sclerosis related) were evaluated from clinical onset to month 6: retinal OCT (Spectralis) every month [thicknesses of peripapilar retinal nerve fiber layer (pRNFLTH) and macular layers)] and best-corrected high contrast, low contrast (LCVA) and color visual acuity (CVA), and visual field testing (VF) every 2 months.

Results: After 6 months, pRNFLTH decreased 39.6 µm and macular thickness 14.8 µm. Most pRNFLTH decreased in first 2 months while macular thickness decreased along 3-6 months: thickness of inner macular layers [RNFLTH and ganglion cell layer + inner plexiform layer complex thickness (GCIPTH)] decreased monthly (specially in first 2 months), for outer layers increased in first 2 months, decreasing by months 3-6. GCIPTH change at first month predicted visual impairment at month 6: decrease >4.5 µm (6.5%) poor LCVA, and > 7 ?m (10%) poor VF and CVA .

Conclusions: retrograde axonal degeneration and atrophy of ganglion cells develop within 3 months in ON, while outer layers suffer transient compensatory thickening. Atrophy of GCIP after 1 month of clinical onset is predictive of short-term visual disability.

[PS-1.30]

Blood miRNA expression pattern is a possible risk marker for natalizumab-associated progressive multifocal leukoencephalopathy in multiple sclerosis patients

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Multiple sclerosis (MS) is a common inflammatory and degenerative disease causing neurological disability in young adults. Natalizumab was approved in 2006 for the treatment of MS. It is a monoclonal antibody that binds to the "alpha 4 subunit" of integrins, expressed in activated T cells and other mononuclear leucocytes, blocking their adhesion to the endothelial cells. Thus, their migration into the central nervous system (CNS), a necessary event to trigger the autoimmune attack that causes the demyelination, is inhibited. Long-term therapy has been associated with a higher risk of developing progressive multifocal leukoencephalopathy (PML), a severe demyelinating disease of the CNS caused by a reactivation of a latent infection of the JC virus. Although the global risk can be stratified according to three factors, a biomarker to assess the individual risk is lacking.

We measured the expression of 754 microRNAs, small non-coding RNAs that regulate gene expression, in the blood from 19 natalizumab-treated MS patients during therapy period.
We found differential expression of three miRNA after 12-month therapy between two patients who developed PML after more than two-years therapy and those who did not. Remarkably, this difference was observed prior to the onset of PML, which is very valuable when evaluating the individual risk and continuity of the treatment.

Therefore, we suggest three miRNAs as possible biomarkers for the individual PML risk assessment.

[PS-1.31]

Prenatal exposure to organochlorine compounds and early neuropsychological development, controlled by social environmentT

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Hexachlorobenzene (HCB), Dichlorodiphenyldichloroethylene (p,p'DDE) and Polychlorinated Biphenyls (PCBs) are Organochlorine Compounds (OCs); characterized as persistent, bioaccumulative, and toxic environmental pollutants with potential neurotoxic effects for early neurodevelopment. The aim was to assess prenatal levels of OCs, associated with early neuropsychological development. Our sample was a population-based birth-cohort recruited between 2006-2008 from Zumarraga Hospital, derived from the INMA (INfancia y Medio Ambiente [Environment and Childhood]) project. The main analysis were based on 401 mother- child pairs with complete information on prenatal levels of OCs (collected both in maternal serum during pregnancy and newborn?s umbilical cord serum) and child neuropsychological development (assessed with Bayley Scales of Infant Development) at 26 months. Using multivariate linear regression models, we adjusted for main predictors of neuropsychological development and potential confounders, including social-familiar environment quality. We found that all three prenatal OCs levels studied, both in maternal serum and in newborn cord serum, were related with a subclinical-impairment of motor development. An average of 7 points decrease in Bayley motor scores (in between 5-9 points lost), were associated with each increase of 10 units in prenatal OCs levels. No effects on cognitive development were found. These results suggest that a potential neurotoxic effect of OCs may be evident even at a population-based children-cohort with low dose exposure.

[PS-1.32]

A longitudinal approach to the influence of oxidative stress in cognition in affective and non-affective psychosis

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STUDY OBJECTIVES
To examine the association of baseline total antioxidant status (TAS) and glutathione (GSH) levels with short and long-term cognitive functioning in patients with early onset first-episode psychosis (FEP), comparing affective and non-affective psychosis

SUBJECTS AND METHODS
80 patients (9-17 years) with a FEP and 97 healthy controls were included in the study.
Blood samples were taken at admission for measurement of TAS and GSH and cognitive performance was assessed at baseline and 2 years after.

Linear regression analysis was used to assess the relationship between TAS or GSH levels ar baseline with cognitive performance at both time points, controlling for confounders (tobacco use, antipsychotics consumption and socioeconomic status)

RESULTS
We found a significant relationship between baseline TAS and cognition, both at baseline and 2 years after, in the whole sample. By cognitive domain, oxidative stress appeared exert influence in attention and working memory at baseline, and in attention and memory at the 2 years assessment time.
Exploring the results by diagnostic group only the non-affective patients showed the relation between oxidative damage and cognition.

CONCLUSION
The insult of oxidative stress in cognitive performance affects affective and non-affective psychotic patients in a differente manner, both at baseline and 2 years after the illness onser, being present only in the group of non-affective psychosis.

[PS-1.33]

Genes, neurophysiology and cognition in patients with schizophrenia

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Schizophrenic patients have some cognitive impairments and this deteriorate performance correlates with some neurophysiological abnormalities. The aim of this study is to analize the cognitive impairment in patients with schizophrenia and whether this worse cognition is related to neurophysiological function and the presence of certain genes.

We recruited 29 patients and 28 controls matched by age, gender and educational level. We collected blood of all participants, analizing the alleles for these genes: GRIN1, GRIN 2A, GRIN 2B, NRG1, EAAT3, COMT. All patients and controls were evaluated with a cognitive battery (Brief Assessment of Cognition in Schizophrenia: BACS) and went through an electroencephalografy with P300 test.

We found that two SNPs, related to glutamate transporter and to NMDA, were more frecuent in patients with schizophrenia than in controls. The CI in the patients was significally lower than in controls (82,24 vs.102,78; t=5,090; p<0,001). The patients performed worse than the controls in all cognitive scales (verbal memory, working memory, motor speed, verbal fluency, processing speed and problem resolution). There was a negative correlation between verbal memory and cortical noise in patients with schizophrenia. COMT, GRIN2a, NRG1C genes were associated with worse performance in cognitive test (memory and problem resolution).

The are some genes that are implicated in some endophenotipes of schizophrenia and the localization of these genes could be a key to early diagnosis.

[PS-1.34]

Plasma levels of olanzapine: influencing variables and clinical response in First-Episode Psychosis

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Objectives:
a)To see which variables influence plasma levels in a sample of First-Episode Psychosis (FEP) patients. b)To determine the validity of olanzapine plasma break-points previously proposed as clinical predictors of response to treatment.

Methods:
Twenty-five FEP patients who had plasma concentrations of olanzapine and clinical measures at 2 and 6-month follow-up were studied.

Clinical response to olanzapine was defined as ≥20% reduction in PANSS scores from baseline. Plasma levels were quantified using HPLC-tandem mass spectrometric detection methods(LC/MS/MS). A mixed-effects linear regression model for olanzapine plasma levels with weight, age, gender, cigarettes/day, dose, antidepressants, and ≥20% improvement in PANSS as covariates was performed. The plasma break-points we considered were the ones referred by Perry et al.(1999) and Fellows et al.(2003).

Results:
Mean age was 28.39(SD=7.75). Daily doses ranged from 2.5 to 20mg/day. Blood samples were obtained 10.53(SD=1.08 hours) after last intake. The following variables resulted significant: age(beta=1.02;p=0.028); cigarettes/day(beta=-0.81;p=0.023); and dose(beta=3.09;p=<0.001). The ≥23 ng/ml break-point identified 89% of responders at month 2 and 76% at month 6, whereas 100% of non-responders were plotted above it.

Conclusions:
Age, number of cigarettes and dose may contribute to explain variability in Olanzapine plasma levels. The aforementioned plasma concentration break-point had high sensitivity but no specificity. We propose the use of more strict criteria for clinical response(e.g.40% PANSS reduction) to increase specificity.

[PS-1.35]

Is therapeutic drug monitoring of risperidone a useful tool to predict clinical response and side effects in first-episode psychosis?

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Purpose:
To investigate in a sample of first-episode psychosis(FEP) patients the relationship between dose, and plasma concentrations of risperidone and its association with clinical efficacy and side-effects.

Methods:
Twenty-one FEP patients treated with risperidone who had plasma concentrations and clinical measures at month 2 were selected. Clinical data were obtained using standardized rating scales. Plasma levels were quantified by HPLC-tandem mass spectrometric detection methods(HPLC/MS/MS). Correlation analyses and mixed-effects regression models were performed.

Results:
Mean age was 26.5(±5.7), and mean oral dose 4.7mg/day(±1.6).Although a correlation was found between dose and 9-OH-risperidone concentrations (r=0.563,p=0.008) -risperidone?s active metabolite-, no other association was detected between dose and risperidone or active moiety levels (risperidone plus 9-OH-risperidone). The mixed-effects model for 9-OH-risperidone levels confirmed that, aside from the dose (beta=4.23,p=0.007), no other variable resulted significant in predicting 9-OH-risperidone concentrations (age, gender, weight, cigarettes/day, cotinine levels, and consumption of antidepressants). No correlation was found between percent decrease in total PANSS or scores in UKU-Side-effects Rating Scale and plasma levels of risperidone, 9-OH-risperidone or active moiety.

Conclusions:
Risperidone is rapidly metabolized to 9-OH-risperidone, so the majority of patients showed higher concentrations of 9-OH-risperidone than of risperidone. Therefore, 9-OH-risperidone concentrations may be more representative of the dose. However, it does not appear to be any association between plasma concentrations of risperidone, its metabolite, active moiety and clinical improvement or side-effects.

[PS-2.1]

Altered presynaptic and postsynaptic transmission in Dorsal Raphe neurons of GIRK2 knockout mice

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We examined the involvement of G-protein-coupled inwardly rectifying potassium (GIRK) channels in 5-HT, GABAergic and glutamatergic synaptic activity in Dorsal Raphe (DR) neurons of mice lacking Girk2 gene. Thus, whole-cell patch-clamp experiments were performed in DR slices examining outward currents evoked by 5-HT1A (5-CT) and GABAB receptors (baclofen) agonists, as well as the spontaneous and evoked excitatory and inhibitory postsynaptic currents.

In wild-type mice, 5-CT and baclofen elicited outward currents that were largely diminished in GIRK2 knockout mice. Regarding presynaptic GABA release, the frequency and amplitude of sIPSC were significantly decreased and the number of neurons which showed paired-pulse facilitation of eIPSC was significantly greater in DR of GIRK2 knockout mice. Then, we investigated whether this difference in GABA release was due to an altered 5-HT transmission. The 5-HT1A antagonist, WAY100635 produced an increase in the frequency of sIPSC in wild-type mice that was significantly smaller in GIRK2 knockout group. Presynaptic release of glutamate remained unaltered in the mutant mice. This study demonstrates that in DR, GIRK2 channels are the main inhibitory effectors of the postsynaptic actions of 5-HT1A and GABAB receptors. Moreover, Girk2 gene deletion reduces GABA release in DR neurons by affecting 5-HT transmission.

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[PS-2.2]

A new memory specific adenylyl cyclase in Drosophila olfactory memory

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The cAMP/PKA pathway is a critical pathway in memory formation from invertebrate to vertebrate systems. In Drosophila, the cAMP pathway is activated in the mushroom body (MB) during olfactory memory formation, in which an odor is paired with electric shock punishment that leads to a learnt avoidance of the associated odor. The MB is the main associative learning and memory center in insects and in Drosophila it is composed of three main subpopulation of neurons: alphabeta, gamma and alpha'beta'. The distinct morphologies and expression profiles of each subpopulation suggests that they play different roles in memory formation.
In the MB, G-protein-coupled receptors (GPCR) are activated by the unconditioned stimulus (shock), during the classical olfactory conditioning, which activates an adenylyl cyclase (AC) leading to the increase of cAMP second messenger. This effect is potentiated by the synergistic activation of the AC by Ca2+/CaAM through the conditioned stimulus pathway (odor). The cAMP then activates its downstream target PKA leading to memory formation.

One of the first described gene involved in Drosophila olfactory learning, rutabaga, encodes for an AC. Rutabaga is the responsible of the coincidence detection of odor and shock information shock information in albabeta and gamma neurons but it has been shown to be dispensable in the alpha'beta' neurons. This suggests that there could be another AC playing the role of a coincidence detector in the prime neurons.

So far, by bath application of dopamine and acetylcholine in in vivo brain imaging, we have found an AC that contributes to coincidence detection in prime neurons. The reduction of PKA activity observed in imaging experiments correlates with a specific behavioral memory deficit. These results suggest that more than one AC could be involved in olfactory memory in Drosophila, possibly in a memory specific manner.

[PS-2.3]

Compensatory mechanism in the age-induced decline of adult hippocampal neurogenesis

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Adult neurogenesis, the process of generating functional new neurons, persists in the subgranular zone (SGZ) in the dentate gyrus of the hippocampus throughout life. During aging, the SGZ neurogenic capacity undergoes a progressive decline, which is attributed to a loss of the neural stem cell pool. However, whether the remaining steps in the neurogenic cascade, namely stem cell proliferative activity, neuronal survival, progenitor migration or neuronal differentiation are also altered during aging, potentially compensating the loss of neural stem cells. In this study, we compared the SGZ niche of 1, 2, 6 and 12 month-old age mice to assess all phases of neurogenesis. In concordance with previous reports, we observed a dramatical decline in proliferation with increasing age but no major alterations in the survival and differentiation rates. Our data suggest that the strong age-related neuronal loss is not counteracted by any compensatory mechanism, neither of stem cell proliferation, or newborn cell differentiation and survival. Therefore, the age-related decline in neurogenesis is largely explained by the loss of neural stem cells alone.

[PS-2.4]

Lizard visual function is partially recovered after optic nerve axotomy

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Significant regeneration of retinal ganglion cell axons occurs after optic nerve transection through a permissive glial scar in Gallotia galloti. Although several of the cellular and molecular events underlying this process have been studied by our group, the functionality of the system has not been tested until now. The pupillary light reflex, accommodation and head orienting have been also used in other reptiles to test visual function (Dunlop et al., 2004). We examined 18 lizards at 3, 6, 9 and 12 months after transection. Our results revealed a tendency of eyelid closing within the first months after operation. Interestingly, by 6 months we detected a significant recovery of pupillary light reflex in two thirds of specimens including a robust response in 17 of them. However, visually guided behaviour recovery was observed only in 2 specimens, yet when presenting a prey (mealworm) in the right, affected eye, most lizards (89%) did not constrict the pupil to focus nor did they follow it as it moved, a behaviour which was detected in the unlesioned side. We conclude that a partial recovery of the visual pathway functionality takes place spontaneously in adult G. galloti, which could be enhanced by training or pharmacologically.

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[PS-2.5]

Nociceptors differentiation from human pluripotent stem cell follows ontogenesis of embryonic sensory neuronal development

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Human embryonic stem cells (hESCs) and the induced pluripotent stem cells (hiPSCs), collectively known as human pluripotent stem cells (hPSCs), represent an invaluable opportunity to dissect complex cellular and molecular events that occur during early nociceptor development. Importantly the differentiation process from hPSCs allow the unique means to track and isolate intermediate cells (precursors) that only transiently exist in vivo like the neural crest cells and progenitor cells for the peripheral nervous system. While specification of peripheral sensory neurons has been studied in animal models, investigation into the embryonic determinants for the emergence of human nociceptive sensory neurons remains elusive. Here we present a study cataloguing the hierarchical differentiation and lineage relationship of sensory neurons, nociceptors and smooth muscles as they are generated from neural crest cells (NCCs) of the hPSCs. Molecular programs leading to the emergence are delineated by the temporal appearance of dorsal neuroepithelial and truck NCCs identities and early embryonic dorsal root ganglion markers. Early during differentiation (day 0), neuroepithelial cells derived from hPSCs stained positive for p75, HNK1, A2B5 and MAP5. The neuroepithelial cells were also positive for BRN3a, however were localized in the perinuclear region as opposed to discreet punctuated pattern later during the differentiation (days 25-30). We also observed two waves of SOX2 expression peaking at days 0-4 and days 18-30. Interestingly at day18, we observed a mutually exclusive localisation of high SOX2+ and high BRN3a+ neurons. By day 30, the neurons were positive for PERIPHERIN, TRKA, Nav1.7 and Nav1.8 channels. TRKA+ neurons were positive for Nav1.7 and Nav1.8, however Nav1.7 staining in the soma was co-localised with TRKA, while this arrangement was not observed along the axon. As for Nav1.8 positive neurons, TRKA did not co-localise with the TTX-R channel neither in the soma nor the axon. Whole cell recording revealed two types of Na currents, a fast gating and voltage dependence component showing TTX sensitivity or typical slow gating Na currents with persistent properties.

[PS-2.6]

Study of acetylcholinesterase and other membrane-bound proteins in cell membrane microarrays of MPTP treated non-human primates, an animal model of Parkinson´s disease

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Parkinson´s disease (PD) is a neurodegenerative disorder that affects around 6.3 million people worldwide. PD is characterized by the loss of dopaminergic neurons, although other neurotransmitter systems are also altered. The causes of PD are still unknown but some neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), induce a rapid onset of Parkinsonism. In this context, the non-human primate, Macaca fascicularis, chronically treated with MPTP is one of the most robust animal models of PD, due to the behavioral and neuroanatomical similarities to human. However, the intrinsic difficulties of working with this specie restrict its use. To overcome these limitations, the cell membrane microarrays technology was applied as it enables to carry out several studies reducing enormously the sample amount. Thus, membranes of different brain regions from control and Parkinsonian monkeys were printed over a slide and the acetylcholinesterase (AChE) activity was determined, as well as the expression of some neuronal markers such as GDNF family receptor alpha-1 and amyloid precursor protein (APP). The MPTP treated monkeys showed an enhanced activity of AChE in the substantia nigra, as it happened in corpus callosum where an increase in the APP expression was also observed.

These results demonstrate the great potential of this platform for studying not only the protein expression levels but also the enzymatic activity with time, sample and cost-saving.

[PS-2.7]

Melusin, CD9 and FRZB show mutual expression regulation and are implicated in the B1 integrin isoform substitution process which is impaired in LGMD2A myotubes

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Background: Limb girdle muscular dystrophy type 2A (LGMD2A) due to mutations in CAPN3 is one of the most common autosomal recessive limb girdle muscular dystrophies. Microarray analysis showed that several genes are deregulated in muscle of LGMD2A patients, but it remains unclear which changes are relevant to the muscle degeneration process. Objective: To unveil whether the altered expression pattern in muscle of LGMD2A patients is replicated in other tissues (blood, skin fibroblasts and myoblasts/myotubes), and to analyze the implication of commonly regulated genes in the pathophysiology of LGMD2A. Results: As reported for muscle, melusin, CD9 and FRZB were upregulated in fibroblasts of LGMD2A patients. Melusin and CD9 are known to interact with B1 integrins, and LGMD2A myotubes showed altered B1 integrin isoform replacement. Although melusin, CD9 and FRZB have not been described to directly interact, our results indicate that in vitro they are related at expression control level. Furthermore, melusin and FRZB also controlled integrin B1 isoform replacement. Conclusion: The derregulation of melusin and FRZB could modify the integrin B1D recruitment in LGMD2A, thereby perturbing the interaction of premyofibrils with the extracellular matrix and signal generation. Moreover, since the upregulation of FRZB inhibits the Wnt pathway, its deregulation could trigger the failed myogenesis in LGMD2A. Therefore, the regulation of these genes might constitute a therapeutic alternative in the treatment of muscular dystrophies.

[PS-2.8]

Characterization of the cellular prion protein in human neurons derived from pluripotent stem cells and in induced neurons

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Transmissible Spongiform Diseases that affect animal and humans are fatal neurodegenerative diseases for which there is no available therapy. Creutzfeldt - Jakob Disease, Fatal Familial Insomnia and the Gerstmann-Sträussler-Schinker affect humans. These diseases can be sporadic, hereditary or infectious, present long incubation periods with no clinical signs or symptoms. The pathogenic agent is the Prion Protein (PrPSc) and is normal form is the cellular protein (PrPc).

It has been possible to replicate prions in cell cultures that overexpress murine or ovine PrPc, indicating that the replication capacity of prions depends partly on the expression levels of endogenous PrPc and on the sequence identity between prion and PrPc expressed into the cells. In the current study we aim to establish a human in vitro cellular model able to support replication of human prions taking advantage of cell reprogramming technology. We have characterized the temporal profile of PrPc expression in human neurons derived from pluripotent stem cells and induced neurons obtained through direct transdifferentiation from human fibroblast; noticing a good PrPc expression levels in both kinds of neurons at different days confirming a robust expression from div 20 onwards. Therefore, the cellular model will be useful both for mechanistic and therapeutic studies.

[PS-2.9]

Protein kinase CK2 and JNK modulate pro-apoptotic effector activation in AMPA-induced excitotoxicity in oligodendrocytes

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Casein kinase 2 (CK2) is a ubiquitous serine-threonine kinase involved in a multitude of cellular processes through modulation of numerous substrates, mostly proteins related to cellular survival/death signaling. CK2 activity has been found to be significantly enhanced in many human and experimental pathologies and increasing evidence links CK2 to the dual function of pro-survival and apoptotic pathways. To analyze the role of CK2 in the functional control of survival/death, here we have investigated the involvement of CK2 in AMPA-induced excitotoxicity using rat cultured oligodendroglial cells. Thus, we observed that two CK2-specific inhibitors, TBB and DRB, attenuated mitochondrial dysfunction and subsequent cell death provoked by brief and moderate AMPA receptor stimulation in oligodendrocytes. Specifically, the CK2 inhibitors, through changes in the phosphorylation levels, modulated the Bcl-2 family protein activation and their redistribution between cytosol/mitochondria/nucleus, modifying the apoptotic properties of these molecules.

Additionally, the moderate stimulation of AMPA receptors in oligodendrocytes caused an early and potent increase in the phosphorylated-JNK levels, and JNK inhibitor SP600125 prevented the activation of BH3-only proteins and finally, protected oligodendrocytes from AMPA-induced excitotoxicity. Together, these results show that CK2 and JNK-dependent pathways are key regulators of AMPA-induced phosphorylation/activation of Bcl-2 family proteins, mitochondrial dysfunction and cell death in cultured oligodendrocytes and suggest that modulation of this signaling may help in developing novel drugs with therapeutic potential for demyelinating diseases.

[PS-2.10]

Altered mitochondrial dynamics in neurons from Parkinson disease patients with mutations in PINK1

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Several genes associated to PD, namely PINK1 (PTEN-induced kinase 1), LRRK2 (leucine-rich repeat kinase 2) and alpha-synuclein, activate pathogenic pathways that converge in mitochondrial dysfunction. In this study, we reprogrammed skin fibroblasts from patients with PD-associated mutations in PINK1 that inactivate kinase function to generate patient-specific iPSCs (induced pluripotent stem cells). PINK1-iPSCs were differentiated into dopamine neurons, which are lost in PD. Confocal analysis of mitochondrial morphology revealed a highly fragmented network that was not observed in patient-derived fibroblasts. Fission proteins were upregulated in the fibroblasts but not in neurons, suggesting that fibroblasts can compensate the PINK1 defect. Next, we characterized the expression of alpha-synuclein, which inhibits mitochondrial fusion. There was no difference between control and patient-derived neurons at the times examined, suggesting that the increased fragmentation is not caused by dysregulation of alpha-synuclein. Accordingly, over-expression of alpha-synuclein did not modify RNA levels of the fission proteins. In contrast, we found a remarkable increase in LRRK2 both at RNA and protein levels in patients' fibroblasts and neurons with PINK1 mutations. Currently, we are testing the effect of LRRK2 knockdown and wild-type PINK1 over-expression in patients' cells to mechanistically define the observed alterations. Since we have detected increased mitochondrial fragmentation also in PD-associated LRRK2 mutations we propose that dysregulation of mitochondrial dynamics is a common pathogenic event in multiple forms of PD.

[PS-2.11]

Understanding the structure and functions of perineuronal nets in enhancing regeneration and plasticity in the CNS

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Chondroitin sulphate proteoglycans (CSPGs) has been widely reported in the central nervous system (CNS) and their up-regulation in the glial scar after injury is a strong deterrent to regeneration. Removal of CSPGs in the lesion area successfully restores functional recovery. Recently, CSPGs are also reported in a highly aggregated structure called perineronal nets (PNNs) which are important to plasticity in the brain. PNNs wrap around the neuronal surface and are found circumferencing synapses. To understand the molecular assembly of the aggregates and their corresponding contributions to the PNNs, we created an in vitro model for the PNNs. While hyaluronan, link proteins, tenascin R and aggrecan (a CSPG) are the key components for the assembly of the PNNs, the sulphation modification(s) on the CSPGs is important in controlling the binding of functional effectors to the PNNs. With the use of link protein knockout mice, we subsequently observed that the mice retain juvenile plasticity in the visual cortex till adulthood. We also demonstrated that one of the PNN effectors semaphorin 3A binds specifically to chondroitin sulphate E (CS-E) with C-4,6-sulphations. Blocking CS-E epitopes using anti-CS-E antibodies partially neutralises this binding and renders the PNNs less inhibitory in vitro. These results suggest that manipulation of PNNs by their assembly or sulphation may be useful in enhancing plasticity after injury in the CNS.

[PS-2.12]

Variations in whole-brain functional connectivity across seizure chronification in a mouse model of mesial temporal lobe epilepsy

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How does the brain become epileptic? Although this is a major question for modern Neurology, we do not have yet a proper answer. Despite of intense research in the field, epilepsy continues having today a high prevalence, still the only available treatments are merely palliative, and a large number of patients are pharmaco-resistant and require surgical removal of the epileptogenic area. To go further to the answer of this question, we propose here to address what are the changes in the pattern of functional connectivity (FC) occurring during the transformation from a healthy brain into an epileptic brain. To answer this question, we have analyzed longitudinal variations of FC patterns in the hippocampus in a mouse model of medial temporal lobe epilepsy (MTLE), induced by intra-hippocampal injection of kainic acid (KA), which resembles main features of human MTLE. Mice were implanted with bilateral intrahippocampal and intracortical electrodes immediately after the injection of KA, and discontinuous 4h video EEG recordings were obtained up to 42 days post injection. Data was converted to ASCII and postprocessed to calculate two different measures of FC: Network Synchronization Index (NSI), which is based on correlations, and the Interaction Information (II), a generalization of the mutual information to triplets to address the amount information (redundancy or synergy) bound up in the set of three variables. The two measures, NSI and II, were computed across the time-evolution of the disease and across different frequency bands. We found important differences in preictal and postictal states in comparison to the baseline pattern of inter-ictal activity, regarding the strength of synchronism and the amount of redundancy and synergetic interactions. In particular, we noticed that whilst the time-evolution of the FC pattern for low-frequency bands evolved with the severity of the disease, this did not happen for the time-evolution of synergy and redundancy, suggesting that the information character of the epileptogenic network was affected in a non-linear manner with the disease severity.

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[PS-2.13]

Parkin, Mitophagy and Parkinson's Disease

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Mitophagy is a type of autophagy by which defective mitochondria are selectively targeted and degraded. PINK1 and Parkin are master regulators of mitophagy and mutations in these genes cause Parkinson's Disease (PD). How mitophagy is regulated and the mechanism by which its failure may cause PD is yet unclear. We are studying Parkin-dependent mitophagy using in vitro and in vivo models. Using RPE1 cells that stably overexpress YFP-Parkin we studied how mitophagy happens after CCCP treatment and checked for genes that modify this process. Our studies show that Parkin overexpression (in RPE1-YFP-Parkin cells) causes cell death when mitophagy is triggered with CCCP treatment, as compared to parental RPE1 cells. We also have overexpressed WT and Catalytic Inactive (CI) dParkin in Drosophila neurons. Reduced longevity and locomotor deficits appear when WT dParkin is overexpressed in Drosophila neurons. Further characterization of the effect and mechanisms regulated by Parkin could help to understand better what happens in patiens with PD.

[PS-2.14]

Overexpression of constitutively active forms of small gtpases of the rho family modify neuronal morphology.

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Small GTPases of the Rho family are key players in complex signaling networks that control normal activity in most if not all cell types. Like other small GTPases, Rho GTPases function as molecular switches to control celular signaling pathways. They are present in two conformations, an inactive and other active. In their active configuration, GTPases of the Rho family are best known for controlling the appropriate actin cytoskeleton reorganization in response to extracellular signals, although their implication in additional biological processes, such as gene expression regulation, cell polarity and cell migration have also been reported. Functional specificity of small GTPases of the Rho family in intracellular signaling pathways depends mainly on the cellular system, type of stimuli and their intracellular localization. Regarding the nervous system, small GTPases of the Rho family participate actively controlling cytoskeleton dynamics in neurons, thereby modulating synaptic plasticity. We have explored the effect produced by the overexpression of the constitutively active forms of RhoA, Rac1 and Cdc42 on the actin cytoskeleton in primary neurons. After 5, 10, 15 y 17 DIVs, we have observed that the overexpression of RhoA and Cdc42 produce a dramatic contraction of dendrites and axons, causing a rounding of the neurons. Unlike the RhoA, Cdc42 induces the formation of an actin pericellular structure whose appearance resembles a combination of filli-lamellipodia. In addition, Cdc42 induces an unusual repositioning of the cell nucleus. However and in contrast to RhoA and Cdc42, overexpression of constitutively active Rac progressively leads to neuronal death.

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[PS-2.15]

Investigating resting state functional connectivity in bilingual and monolingual infants with near infrared spectroscopy

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Resting state functional connectivity (RSFC) networks reflect synchronized spontaneous activity of spatially distant areas in the human brain and are essential to understand the intrinsic relationship between brain regions that are functionally related in adults and infants. In this work, we investigate if the presence of long-term environmental factors such as the exposure to two languages at early age could lead to changes in these networks. A 52-channel near-infrared spectroscopy (NIRS) system was used to measure spontaneous cortical activity in 4-month-old monolingual (N=11) and bilingual infants (N=17). Correlation coefficients for the time course of oxygenated haemoglobin signal were determined to construct the connectivity matrix for each participant. Potential significant connections present in each group and differences in the connectivity patterns between groups were examined by means of parametric and non-parametric permutation statistical methods. Network metrics of intrahemispheric and interhemispheric connectivity were also evaluated. Our results for bilingual infants showed a large number of intrahemispheric and interhemispheric connections especially over frontal and temporal regions, while monolinguals showed less connections and a different connectivity pattern with most connections being localized in frontal and occipital regions. This suggests that early and continued exposure to a bilingual environment might require the participation of additional brain areas and that this extra activation might influence the configuration and the development of resting state functional brain networks.

[PS-2.16]

Does orthographic depth influence non-linguistic processing?

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Orthographic depth, or the relative consistency of letter-to-sound mappings, has been proposed to result in differences in reading strategies across languages. To investigate whether the influence of learning the grapheme-phoneme conversion rules of a language also extends to non-linguistic processes, we tested children learning to read as well as proficient readers of Spanish (consistent) and French (inconsistent). Participants completed two phases, learning and test. During the learning phase they were presented with tone-shape pairs, the tones being either consistently paired with one shape (simple rule) or with two different shapes (complex rule). During both phases, participants pressed the button corresponding to the tone, while also being presented with a task-irrelevant shape. Critically, test phase trials were either congruent or incongruent with the tone-shape pairings acquired in the earlier learning phase. It was expected that, before being confident of the grapheme-phoneme conversion rules in their languages, both groups should behave similarly. In contrast, proficient readers were expected to differ, with French readers showing an equally large incongruency effect for simple and complex pairings (indicating the acceptance that one sound can be mapped onto two different shapes), while Spanish readers should learn only the simple but not the complex rule, in line with their reading experience (i.e. the one-to-one correspondence of letters and sounds in Spanish). Results and implications will be discussed.

[PS-2.17]

Mixing languages in a bilingual learning context: beneficial or detrimental?

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Traditionally, formal education in bilingual societies has followed the one-subject-one-language motto, assuming that only one language should be used during the tuition of a given academic subject to prevent for any possible difficulty associated from an incorrect conceptual representation as a consequence of mixing languages. The current study was aimed at investigating whether the use of two vehicular languages as compared to a single one harms the integration of new concepts, or alternatively, whether an educational model based on the regular mixing of two languages during instruction should be favored. Spanish-Basque bilingual children and adults were tested in a series of experiments in which they had to learn some novel concepts represented by unknown objects associated to definitions of existing and known objects of daily life. Half of the subjects completed the learning phase in a single-language context, while the other completed it in a dual-language context. Several indirect and direct measurements of learning, conceptual representation and integration were collected. Results from both adults and children showed that language-mixing contexts were not detrimental for the learning process. These data showed no significant differences between groups, yielding the conclusion that mixing languages provides learners with enhanced communicative skills in the full absence of any detriment in concept acquisition.

[PS-2.18]

Atypical neural synchronization to auditory stimuli in adults and children with and without dyslexia: an MEG study

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According to the Asymmetric Sampling in Time theory, hemispherical asymmetries in the neural structure of the auditory cortex make the left hemisphere more sensitive to short timescales (25-50 ms: ~40 Hz) and the right to longer timescales (250 ms: ~4 Hz). Inappropriate sampling of the auditory signals could be responsible for the phonological difficulties of dyslexia. Previous studies reported both weak left hemisphere synchronization for fast oscillatory components of speech and weak right hemisphere synchronization for slow oscillations. No study evaluated both low and high frequency synchronization in the same population.

We focused on a different linguistic population (Spanish monolinguals with and without dyslexia) and evaluated how these effects change with age (studying both adults and children). Magnetoencephalographic activity was recorded whilst participant watched a silent movie and hear stimuli presenting amplitude modulated noise at low (2, 4, 7 Hz) and high frequencies (30, 60 Hz).

Our results indicate that both children and adult dyslexic´s present differences at high frequencies compare to their corresponding matched groups, suggesting that synchronization effects are a consequence of how language impacts on dyslexia. Furthermore, in dyslexic children low frequency differences seem to play an important role too, indicating that the auditory synchronization phenomenon changes with age.

[PS-2.19]

The development of sound-shape correspondence effect in infants

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Sound-shape correspondence represents a bias associating acoustic (name) and visual (shape) information. A well-known example, shown with adults and toddlers, is association of the pseudo-word kiki with angular objects, and the pseudo-word bouba" with rounded objects. However, studies in preverbal infants show contradictory results. The first experiment aimed to replicate the previously found sound-shape effect in 4-month-old (MO) infants. In the preference looking paradigm 4 MO Spanish monolingual and Spanish-Basque bilingual infants were exposed to congruent trials (buba presented with angular objects/"kike with rounded objects) and incongruent trials (kike with rounded objects/bubawith angular objects). The results did not replicate previous finding, showing no significant difference between congruent and incongruent trials. The second experiment examined whether language specific stimuli can elicit the sound-shape effect. Using the same paradigm, another group of 4 MO Spanish monolingual infants were presented with Spanish-like pseudo-words: racetofor angular and bubano for rounded objects. The results again did not show difference between congruent and incongruent trials. Our results from two experiments show no evidence for sound-shape correspondence in 4 MO infants. One of the reasons can be poor multisensory integration between auditory and visual information at that age. Our next study examine the sound-shape effect in 12 MO infants when multisensory integration is more developed. The preliminary results in relation with previous findings will be discussed.

[PS-2.20]

Look at my face and tell me what's written... if you can!

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Reading is a learnt skill that entails structural and functional brain changes. Recent research has demonstrated that these changes are mainly due to a progressive specialization of a left inferior occipito-temporal region becoming increasingly responsive to visual words. This region, a critical node of the reading circuitry, has been suggested to develop from a partial recycling of a cortical territory evolved for object and face recognition. Our main goal is to explore the plausibility of the recycling hypothesis in a context where faces and words are presented together competing for the same resources. We combine fMRI and probabilistic tractography information to explore possible functional and anatomical interconnectivity between VWFA and FFA. Critically, we found a clear-cut difference in the response activation of these two regions when comparing responses to the stimuli presented in isolation and stimuli presented simultaneously. Anatomical and functional connections between these two regions were also explored, demonstrating a close structural and functional link between these two critical regions. These results demonstrate the existence of a tight relationship between these two well-differentiated areas, and suggest that in spite of the immutable nature of face-selective areas, which seem to be determined by phylogenetic heritage, word-responsive areas lack this invariable nature and are greatly influenced by the presence of competing visual objects that activate adjoining brain regions, thus supporting the recycling hypothesis.

[PS-2.21]

Neurobiological bases of the testing effect: functional neuroimaging after a week delay

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Retrieval practice compared to study alone increases memory performance, which is known as the testing effect. The neurobiological bases of the testing effect are not clear. In the present study participants were instructed to learn Swahili-English vocabulary word-pairs. During training outside of the scanner, participants were assigned randomly to the study group, which only studied the word-pairs, or to the test group, which both studied and tested the word-pairs. After a week delay, all participants returned for the same final cued-recall test in the scanner. The test group compared to the study group showed enhanced activation for correct > forget trials in left putamen and left supramarginal gyrus. This reflects an enriched representation of the items that facilitate its retrieval. These areas were functionally connected with right putamen and bilateral precentral gyrus, which are areas related with the onset of the verbal answer. In contrast, for the study group compared to the test group, activation was greater in regions throughout the frontal cortex for correct > forget trials. There was an increased functional connectivity of these areas with the bilateral inferior parietal lobe and middle frontal gyrus. The activity and connectivity of these regions are typically related to successful retrieval. These activity pattern differences between groups may be the base of the memory benefit associated with testing effect.

[PS-2.22]

Does lifelong bilingualism alter the structure and connectivity of the brain?

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Our previous study suggested higher-connected and more efficient sub-networks developed by young-bilinguals. These sub-networks comprised mostly regions devoted to language processing and monitoring. However, which aspects of bilingualism contribute to these differences and the exact nature of these sub-networks is unclear. Additionally, how the organization of the brain networks develops over time during bilinguals' lifespan need to be assessed. The aim of the current study was to investigate whether the structural brain network changes over time comparing young and old adults bilinguals and monolinguals. Also to investigate how the age-of-acquisition and proficiency of second-language modify the brain network. To determine between-groups different connectivity patterns we employed DW-MRI tractography techniques and a network-based statistic. Any difference was found between elderly bilinguals and monolinguals. Instead, we found a positive correlation in young bilinguals between age-of-acquisition and interconnectivity in a set of regions (i.e. L_insula, L_precuneos, R_inferior-occipital-gyrus, R_middle-temporal-pole). We also found a negative correlation in old bilinguals between proficiency and interconnectivity in another set of regions (i.e. L_Heschl, R_medial-superior-frontal, R/L_medial-orbitofrontal, R_inferior-orbitofrontal cortex). The bilingual-specific neural sub-networks found in our previous study were not reproduced in these old adults. These could suggest a high-level dynamism and plasticity across lifespan of the neural networks supporting languages. Also, these findings could suggest that these dynamic circuits may be modulated by the age-of-acquisition and proficiency of second-language.

[PS-2.23]

Brain morphometry of Dravet Syndrome

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The aim of this study was to identify differential global and local brain structural patterns in Dravet Syndrome (DS) as compared with a control subject group, using brain morphometry techniques which provide a quantitative whole-brain structural analysis that allows specific patterns to be generalized across series of individuals. 11 patients with the diagnosis of DS (seven with mutations in the SCN1A gene) and 11 well-matched healthy controls were investigated using voxel brain morphometry (VBM) and cortical thickness measurements. Global volume reductions of gray matter (GM) and white matter (WM) were related to DS. Local volume reductions corresponding to several structures: putamen, pallidum, brainstem, the white matter of the right middle frontal gyrus, projection fibers (left anterior thalamic radiation, corticospinal tracts), association fibers (left inferior fronto-occipital fasciculus, left uncinate fasciculus, left cingulum), were also found. Furthermore, DS showed a larger left posterior cingulate cortical thickness. The present findings describe DS-related brain structure abnormalities probably linked to the expression of the SCN1A mutation.

[PS-2.24]

Brain Cloud Computing: Brain image pre-processing made easy and boring

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BCC is a spin-off of the Computational Intelligence Group of the UPV/EHU. Its main objective is to provide assistance and computational support to neuroscience researchers in their data manipulation, from data management to the application of computational algorithms needed to extract publishable results and conclusions. BCC is born from the recognition of the following facts: (a) neuroscience experiments are complex data analysis problems which can benefit from a professional approach in the treatment of the data; (b) neuroscience researchers come from a wide variety of fields, most of them lacking the needed computational science background, hence, much effort goes on mastering tools and methods that could be eased by professional support; (c) researchers are interested in reproducible results obtained through sound methodological approaches in a field that is experiencing fast evolution by new tools, procedures and methods.

We also aim to provide software interfaces with machine learning-based quality checkers and computational resources in an accountable way. This will allow to manage human and computer power to successfully complete research projects. Cloud computing will make it feasible to achieve resource tailoring to the actual needs of the research project. Computer and neuro-scientific staff backed by success stories will make this possible keeping pace with the forefront of the computational technologies applied in neuroscience.

[PS-2.25]

Optimization of the hippocampal segmentation along its longitudinal axis

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The human hippocampal formation is a crucial brain structure for memory and cognitive function that interacts extensively with distributed cortical and subcortical regions. Recent neuroimaging studies have found differences along the hippocampus longitudinal axis in terms of function, structure and connectivity with other regions, stressing the importance of improving the precision of the available segmentation methods typically used to divide this brain structure into anterior and posterior parts. In this regard, current segmentation conventions present two main sources of inaccuracies related to how separating planes along the longitudinal axis are chosen and how the in-scanner head position is corrected and equated across subjects before segmentation. These issues are typically addressed by manually aligning the brain for roll, pitch, and yaw rotations along the inter-hemispheric fissure, AC-PC line and orbits. Here, we propose an automated method based on estimating the longitudinal axis of the hippocampus with principal component analysis. The estimated direction is used to define the orientation of the separating planes, which removes the variability associated with the manual alignment of the in-scanner brain position. Our results show that this automatized procedure minimizes the error generated by the accumulation of manual operations while ensuring better reproducibility of results. This methodological improvement can potentially be used to improve the segmentation of other subcortical structures.

[PS-2.26]

Neuroimaging Methods for Systems Neuroscience and Disease: Insights from Information Theory and Causality

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Contemporary neuroimaging methods can shed light on the basis of human neural and cognitive specializations, with important implications for neuroscience and medicine. Human brain shows properties of both segregation and integration; the first property accounts for its modularity and specialization, whilst the integration is due to the brain connectivity between distinct modules within of the nervous system. In particular, brain connectivity refers to a pattern of anatomical links ("anatomical connectivity"), of statistical dependencies ("functional connectivity") or of causal interactions ("effective connectivity"). In this talk I will describe some approaches which have shown the usefulness of Information Theory for the estimation of brain connectivity from brain data, both for the processing of sensory stimuli and in resting conditions.

[PS-2.27]

Estimation of layer specificity of Spin Echo and Gradient Echo BOLD at 7T

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The blood-oxygen-level dependent (BOLD) signal is a consequence of neural activity and driven by changes in blood volume, flow and metabolic rate of oxygen consumption. Veins perpendicular to the cortex carry blood through and from all the cortical layers downstream from the layer they originate from. Therefore, neural activation in one layer results in a BOLD signal not only in that layer but also in downstream layers.

In this work we developed a simplified model of cortical vasculature to obtain the characteristics of the vasculature at different cortical depths. Based on these characteristics, we modeled the BOLD signal across the cortex as a volume weighted sum of intravascular and extravascular contribution at baseline and activation for Gradient Echo (GE) and Spin Echo (SE) sequences at 7T. We then estimated the contribution of upstream layers in the predicted laminar BOLD.

The results of the simulation show that, under the assumption of equal neural activation and vascular reactivity across the cortical depth, SE-BOLD is rather laminar specific, as it is driven by the vessels in the laminar mesh. GE BOLD, on the contrary, is dominated by ICVs and the spatial specificity of the measured signal is poorer as layers approach the cortical surface, where it is highly inspecific.

Future developments of this work will be aimed at predicting the cortical layer specific PSF of the BOLD signal under realistic activation patterns.

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[PS-2.28]

The contribution of Genome-wide Association Studies to the detection of genes associated to cognitive traits in schizophrenia patients: a review

Hernández-Martín A. [1], Ruiz de Azúa S. [1, 2, 3], García-Fernández S. [1, 2], Haidar K. [2], Fernández M. [2], Ugarte A. [2], García-Alocen A. [2], Bermundez Ampudia C. [2] & González-Pinto A.M. [1, 2]

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The genetic analyses known as Genome-wide Association Studies (GWAS) have proved to be a useful tool to discover genes with a potential influence over psychiatric disorders. The aim of this study is to summarize the latest GWAS findings of genes that affect cognitive processes in schizophrenia patients. We did a systematic review of articles through a search strategy with the keywords "schizophrenia" and "cognition" and "Genome-wide Association Study" or "GWAS". We classified results by detected polymorphisms and the gene they may influence due to proximity. Observed results include association of NRGN and TCF4 to memory and perturbation of pathways involved in brain development; of PTPRO to memory and learning; of WDR72 to executive functioning; of HEY1 to working memory, and of BCAS3, APPBP2 and MGAT5B to spatial memory. Moreover, CSMD1 and CPXM2 among other genes appear linked to IQ, while PKNOX2, MYH13, PHT2 and GPC6 are shown to influence formal thought disorder. A relation between MHC and performance in Wechsler Adult Intelligence Scale (WAIS) and Cognitive Performance Test (CPT) has also been noted. We conclude that GWAS is a valuable method for performing genetic screenings that may help find candidate genes in polygenic disorders with no clear aetiology like schizophrenia. It is necessary, however, to do a subsequent assessment of the candidate genes to test the validity of GWAS results.

[PS-2.29]

Effectiveness of the REHACOP Cognitive Rehabilitation Program in Multiple Sclerosis

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Introduction
Multiple Sclerosis (MS) is associated with impairment in several cognitive functions. Although some studies have attempted to test the efficacy of cognitive rehabilitation in MS, they do not implement an integrative rehabilitation program. The aim of the current study is to test the efficacy of an integrative rehabilitation program in MS.

Methods
Twenty-six MS patients were randomized to the rehabilitation (REHACOP) or control group. REHACOP group (n=15) received cognitive rehabilitation for attention, processing speed, learning and memory, language, executive functions and social cognition for 3 months (3 sessions/week of 60 minutes). The control group (n=16) did not receive any assistance. Patients underwent an extensive neuropsychological assessment at baseline and after treatment that included test of attention, processing speed, verbal and visual memory, working memory, verbal fluency, executive functions, naming and theory of mind. Both groups differed significantly on the MMSE score, so this variable was included as a covariate in repeated measures MANCOVA.

Results
Group by time interactions of repeated measures MANCOVA indicated that the experimental group improved significantly when compared to control group in processing speed (n2p =0.14, p=0.04), working memory (n2p =0.17, p=0.03) and executive functions (n2p =0.13, p=0.05), as well as a tendency to significant improvement in verbal memory (p=0.07).

Conclusions
The REHACOP group showed significant and large improvement in processing speed and working memory, and medium-large improvement in executive functions.

[PS-2.30]

The Predictive Role of Processing Speed deficit in Verbal and Visual Memory in Multiple Sclerosis

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Introduction:
Multiple sclerosis (MS) patients suffer from impairment in several cognitive functions including attention (At), working memory (WM), processing speed (PS), verbal memory (VM) and visual memory (ViM). Previous studies have found an association between At, WM or PS and memory. The aim of this study was to investigate the predictive role of At, WM and PS in VM and ViM in MS and healthy controls (HC).

Methods:
Twenty-seven patients with MS and 27 matched HC underwent an extensive neuropsychological battery. Simple and multiple stepwise regression analyses were performed to examine the predictive relationship between At, PS and WM and VM as well as ViM.

Results:
Simple regressions showed that a significant percentage of the variance of VM was predicted by At (21.5%, $p<0.05$) and PS (30.6%, $p<0.01$) among patients with MS. For ViM, only PS predicted a significant percentage of the variance (25.3%, $p<0.01$). Finally, multiple stepwise regression showed that the unique cognitive function which explains a percentage of VM (30.6%, $p<0.01$) and ViM (25.3%, $p<0.01$) variance was PS. No significant regressions were found in HC.

Conclusion:
In conclusion, taking into account the interaction of the three cognitive domains the unique function that predicts the performance in MS on VM or ViM is PS. These results emphasize the need of include PS training in cognitive rehabilitation programs to improve VM and ViM performance in MS.

[PS-2.31]

Social and basic cognitive functions improvement in Parkinson disease with REHACOP program

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Background:
Mild cognitive impairment is common in non-demented Parkinson disease (PD) patients from the beginning of the disease. The aim of this study is to assess the efficacy of an integrative cognitive rehabilitation program (REHACOP) in PD.

Methods:
Forty-two PD patients without dementia (mean age=67.40 ± 6.60; Hoehn & Yahr stages 1-3; UPDRS=36.80 ± 17.85; years of disease evolution= 6.71 ± 5.40) were randomly divided to either the cognitive rehabilitation group with REHACOP or the control group (occupational activities) for 3 months. Both groups underwent a neuropsychological battery at baseline and after cognitive treatment assessing executive functions, processing speed, visual and verbal memory and theory of mind.

Results:
After receiving cognitive rehabilitation, the REHACOP group improved significantly in processing speed (d=0.80, 95% CI=0.15 to 1.41), visual learning and memory (d=0.76, 95% CI=0.12 to 1.38), theory of mind (d=0.92, 95% CI=0.18 to 1.44), compared to controls. Improvement in verbal learning and memory was only marginally significant (p=0.06). However, no significant changes were detected in executive functioning.

Conclusions:
After cognitive rehabilitation, PD patients improved significantly in specific cognitive domains such as processing speed, visual learning, visual memory and theory of mind. According to these results, cognitive rehabilitation may be useful and may be implemented in the treatment of patients with PD.

[PS-2.32]

Observation of Genotype-Phenotype interaction effects on White Matter in Alzheimer Disease and Bipolar Disorder: a randomized controlled trial

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Background: WM damage is associated with a wide range of neuropsychiatric disorders and influence the prognosis. The mechanisms underlying WM damage is still unknown and recent studies suggest that genetic factors may be contributory. Objective: To analyze how neuregulin 1 (NRG-1) might be involved in white matter damage in Bipolar Disorder (BD) and Alzheimer?s Disease (AD).

Methods: One hundred elderly subjects are included in the present study. The size of the sample has been calculated to obtain a 90% of statistical strenght. Taking into account that the level of statistical significance is 5%. All will be recruited in Santiago Apostol Hospital. Informed consent for participation will be obtained from each subject or an appropriate surrogate (in the case of patients with AD). The subjects will be divided into three groups. The AD group will include 100 subjects fulfilling the NINDS-ADRDA criteria for probable AD. The BD group will include 100 patients fulfilling DSM-IV criteria, and the control group will include 100 healthy subjects without memory complaints. All subjects will undergo a protocol including: 1.-Clinical evaluation; 2.-Evaluation of cognitive, functional, psychological and social domains, with the following variables: KATZ, Lawton, Barthel, NPI, PANSS, YMRS, HDRS-21, GDS, FAST, CDR, BRDS, MMSE, CAMCOG, Wisconsin, Trail Making, Stroop; 3.- Genetic NRG1 study; 4-Volumetric and diffusion tensor MRI.

[PS-2.33]

Cannabis use and involuntary admission may mediate long-term adherence in first-episode psychosis patients

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Background: This study aimed to examine factors associated with treatment adherence in first-episode psychosis (FEP) patients following over 8 years, especially involuntary first admission and stopping cannabis use.
Methods: This prospective, longitudinal study of FEP patients collected data on symptoms, adherence, functioning, and substance use. Adherence to treatment was the main outcome variable and was categorized as good or bad. Cannabis use during follow-up was stratified as continued use, stopped use, and never used. Bivariate and logistic regression models identified factors significantly associated with adherence and changes in adherence over the 8-year of following.
Results: Of 98 FEP patients analyzed at baseline, 57.1% had involuntary first admission, 74.4% bad adherence, and 52% cannabis use. Baseline good adherence was associated with Global Functioning score ($p = 0.019$), Hamilton Depression Scale ($p = 0.017$) and voluntary admission ($p < 0.001$). Adherence patterns over 8 years included: 43.4% patients always bad, 26.1% always good, 25% improved from bad to good. Among improved adherence group, 95.7% had involuntary first admission and 38.9% stopped cannabis use. In the subgroup of patients with bad adherence at baseline, involuntary first admission and quitting cannabis use during follow up were associated with improved adherence.
Conclusions: The long-term association between treatment adherence and type of first admission and cannabis use in FEP patients suggest targets for intervention to improve clinical outcomes.

[PS-2.34]

Generalizability of Pharmacological and Psychotherapy Clinical Trial Results for Borderline Personality Disorder to Community Samples: Results From the 2004-2005 National epidemiologic Survey on Alcohol and Related Conditions (NESARC)

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Background: The present study sought to quantify the generalizability of clinical trial results in individuals with a DSM-IV diagnosis of borderline personality disorder (BPD) to a representative community sample.

Method: Data were derived from the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a large nationally representative sample from the United States population. We applied a standard set of exclusion criteria representative of pharmacological and psychotherapy clinical trials to adults with a DSM-IV diagnosis of BPD (n = 2,231). Our aim was to assess how many participants with BPD would fulfil eligibility criteria.

Results: We found that more than seven out of ten respondents in a pharmacological efficacy trial and more than five out of ten in a psychotherapy efficacy trial would have been excluded by at least one criterion. Having a current history of substance use disorder and a lifetime history of bipolar disorder explained a large proportion of ineligibility.

Discussion: Clinical trials should consider the impact of exclusion criteria on the generalizability of their results. As required by CONSORT guidelines, reporting exclusion rate estimate and reasons of eligibility should be mandatory in clinical trials. As treatment trials of BPD move from efficacy to effectiveness to better inform clinical practice, the eligibility rate must be increased by imposing less stringent eligibility criteria to allow for more generalizable results.

[PS-2.35]

Telemedicine in bipolar disorder

García- Alocen A. [1], Ruiz de Azua S. [1, 4], Martinez-Cengotitabengoa M. [1, 3], Bermudez-Ampudia C. [1], Gonzalez- Ortega I. [1, 2], Ugarte A. [1], Lopez P. [1, 4], Zorrilla I. [1] & Gonzalez-Pinto A. M. [1, 4]

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Objectives
To compare the efficacy of an innovate telemedicine psyeducational treatment (TPT) based on a psychoeducational intervention (21 sessions) with support through telemedicine (12 videos) versus treatment as usual (TAU) based on regular psychiatry review (21 sessions) in a group of bipolar patients.

Methods
38 bipolar patients were randomly distributed in two groups. The psychoeducational therapy was the Colom and Vieta´s program. The telemedicine treatment was performed through the www.puedoser.es web platform provided by Astra Zeneca. In the web platform there are available forums, emails and virtual sessions as a reinforcement of psychoeducation. In order to assess the effectiveness of treatments, FAST scale was administered at baseline and 6 months after the intervention. Both methods were compared using comparative data analysis.

Results
Patients in TPT group had worse daily general functionality at baseline comparing with TAU group ($t=-2.876$; $p=0.008$). The most affected issues were: interpersonal cognitive ($t=-2.611$; $p=0.014$) and interpersonal area ($t=-2.617$; $p=0.014$). After intervention there is an improvement in the general FAST score ($z=-2.74$; $p=0.006$) of the TPT group at 6 months. This improvement occurred mainly in cognitive ($z=-3.24$; $p<0.001$), leisure ($z=-1.85$; $p=0.065$) and interpersonal area ($z=-1.72$; $p=0.086$). No significant improvements were observed in the TAU group.

Conclusion
The TPT support shows to be more effective than TAU in the improvement of general patient functioning of individual with bipolar disorder

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