International
Multi-Brain
Barcelona Congress
Healthy | Pathological | Artificial

Abstract Book

Barcelona, 9-10 November 2022

UNIVERSITAT DE BARCELONA
Institut de Neurociències
UNIVERSITAT DE BARCELONA
EXCELENCIA MARÍA DE MAEZTU

Contents

Silvia Ginés, PhD
Congress Chair

Welcome to the International Multi Brain Barcelona Congress were some of the most talented minds from around the world and across different neuroscience fields will be attended.

As neuroscientist we aim to understand the brain and the nervous system, a curiosity that is driving our research to advance knowledge toward the design of new therapeutics to prevent or halt neurological or psychiatric disorders facing our society. We have a great opportunity to bring different disciplines and take advantage of the different specific research areas to be success in advancing the study of the brain. We hope to increase our knowledge on how to trace brain map connections, develop neuroimaging techniques, identify specific brain populations involved in brain pathologies or to look at artificial intelligence as a powerful tool for diagnostic or even therapeutic aids.

I encourage you to participate in our scientific sessions, lectures, posters and other events at the Multi Brain Congress and seek for interaction with other neuroscientist to increase our capacity to collaborate and innovate together. No doubt that much progress will stem from research presented in this meeting helping to accelerate our ability to make scientific progress and benefit our society.

Thank you being part of the International Brain Meeting 2022.

The “International Multi-Brain Barcelona Congress”, in its first edition, is a pioneering international congress in the integration of three major thematic areas of the study of the brain: the healthy brain, the pathological brain and the artificial brain, with the aim of deciphering the complexity of human brain function.

It will focus on the latest discoveries in the field of neuroscience from a translational perspective: from basic studies in the laboratory, through clinical studies with patients in order to reach the health benefits and knowledge transferred to the whole society.

The main objective of the congress is to bring together neuroscientists from all over the world from different disciplines (Medicine, Psychology, Pharmacy, Chemistry, Physics, Mathematics, Engineering, and Computer Science) and patients (through advocacy societies), to share new scientific discoveries and generate synergies to advance in the whole field of brain knowledge. We are therefore facing an unbeatable meeting point for experts and patients that will provide a benefit to human health, well-being and knowledge.

The event will take place in the incomparable setting of the Paranimf of the Faculty of Medicine of the University of Barcelona (UB), one of the most emblematic buildings of our university.

How to get

Organization Committee

Silvia Ginés, PhD
CONGRESS CHAIR

Associate Professor Department of Biomedicine Faculty of MedicineUniversity of Barcelona

Research line:
EXPERIMENTAL NEUROLOGY, Neuron and glia crosstalk in Huntington's disease.

Jordi Alberch, MD, PhD
DIRECTOR OF THE INSTITUTE OF NEUROSCIENCES

Full Professor Department of Biomedicine Faculty of Medicine University of Barcelona

Research line:
EXPERIMENTAL NEUROLOGY, Neuronal connectivity in Huntington's disease and basal ganglia disorders.

David Bartrés, PhD
FULL PROFESSOR

Department of Medicine Faculty of Medicine University of Barcelona

Research line:
COGNITIVE AND BEHAVIOURAL NEUROSCIENCE, NEUROPSYCHOLOGY, Brain health and neuromodulation.

Mercè Pallàs, PhD
FULL PROFESSOR

Department of Pharmacology, Toxicology, and Therapeutic Chemistry Faculty of Pharmacy University of Barcelona

Research line:
PATHOPHYSIOLOGY OF NERVOUS SYSTEM DISEASES, Neuropharmacology in ageing and Alzheimer's disease.

Petia Radeva, PhD
FULL PROFESSOR

Department of Mathematics and Computer Science Faculty of Mathematics University of Barcelona

Research line:
PATHOPHYSIOLOGY OF NERVOUS SYSTEM DISEASES, Machine learning, Computer Vision, Medical Imaging.

Mel Slater, PhD
DISTINGUISHED INVESTIGATOR

Department of Clinical Psychology and Psychobiology Faculty of Psychology University of Barcelona

Research line:
COGNITIVE AND BEHAVIOURAL NEUROSCIENCE, Virtual environments in psychology and cognitive neuroscience.

Invited speakers

Michael Valenzuela

Co-Founder & CEO of Skin2Neuron Pty Ltd, advisor to WHO Clinical Consortium of Healthy Ageing, and Visiting Professor at Centre for Healthy Brain Ageing, University of New South Wales, Australia.

Michael Valenzuela is a key opinion leader, innovator and creative thinker with a career-long commitment to the prevention and better treatment of dementia. He is unique amongst investigators worldwide to have led research across the fields of stem cells, clinical trials, neuroimaging and cognition.

Dr. Valenzuela studied psychology at the University of New South Wales before completing a PhD on Cognitive Reserve. This work was recognized by one of the nation's top awards, the Australian Museum *Eureka Prize for Medical Research*, and on this subject he has contributed to *WHO Guidelines*, the *Oxford Research Encyclopedia of Psychology* and several international scientific advisory committees.

In parallel, he completed graduate medical school, followed by medical internship training at the Prince of Wales Hospital. In 2012, he established the Regenerative Neuroscience Group at the University of Sydney, and in 2017 became the university's first Professor of Regenerative Medicine.

Michael's group discovered a new method of production of neural precursor cells from human skin, and he is the main inventor on several related patents. On this basis, he co-founded *Skin2Neuron*, a new company that aims to develop the first "anti-dementia" cell therapy for Alzheimer's disease, and is on track to begin human trial in 2024. He now leads this growing biotech as Chief Executive Officer.

In the dementia prevention space, between 2019-2021 Michael served as Project Co-ordinator for ICOPE pilot program, now one of the WHO's flagship initiatives for the UN Decade of Healthy Ageing. He also joined the Centre for Health Brain Ageing at University of New South Wales, continuing his work in computer-based cognitive training, which includes some of the most widely cited studies in the field, invited commentary in The Lancet, and co-design and co-leadership of the $6.5M *Maintain Your Brain* study, the world's largest and most successful dementia prevention trial.

Throughout his career Michael has developed a pipeline of med tech, including *BrainyApp*, the *Brain Training System*, *LOGOS* and *Function_Cloud*. Michael is also a frequent media commentator and author of a popular science book on brain health and dementia prevention, *Maintain Your Brain*.

Míriam Pérez Cruz

Specialist in Fetal Medicine, BCNatal | Fetal Medicine Research Center; Institut de Recerca Sant Joan de Déu; RICORS group. Barcelona, Spain.

Specialist in foetal medicine in BCNatal and Postdoctoral researcher from Sant Joan de Déu Research Institute (IRSJD), Fetal Medicine Barcelona Foundation (Fetal R&D) and RICORS group. The doctor combines medical assistance with the study of "the prenatal origin of adult diseases" and during the last years she has focused in neurodevelopment. The doctor is specialised in foetal neurosonography and foetal echocardiography and her activity in these areas has allowed her to author several scientific articles in this field (Pérez-Cruz et al. 2019 Fetal Diagnosis and Therapy; Masoller et al. Fetal Diagn Ther 2020; Mesa MD et al. Nutrients 2020) and to demonstrate structural brain changes (Hahner et al. 2019 Am J Neuroradiol; Pérez-Cruz et al. UOG 2022; Lip D, Pérez-Cruz et al. in press) and in biochemical markers of brain damage in high-risk foetal population (Escobar, Pérez-Cruz et al. Antioxidants 2022; Abella et al. Int J Environ Res Public Health 2022; Ribera et al. BMC Pediatr 2019; Sánchez-Infantes et al.International Journal of endocrinology 2018). Dr. Pérez Cruz coordinates the prenatal research line "Neurodevelopment in Congenital Heart Disease" from BCNatal of which an article has recently been published showing that foetuses with congenital heart disease have smaller corpus callosum (Pérez-Cruz et al. UOG 2021), possibly as a consequence of the alteration of myelination due to the increase in oxidative stress recently observed by our group in congenital heart disease (Escobar, Pérez-Cruz et al. Antioxidants. 2022). The doctor has recently been awarded a FIS grant PI22/00754 " GrowingBrain: fetal brain reference values for early identification of altered neurodevelopment of prenatal origin.

Sandra Acosta

Assistant Professor (SerraHunter) in Pathology and Experimental Therapeutics, UBneuro, University of Barcelona, Spain.

Dr. Acosta is a developmental neurobiologist interested in undertaking how the human brain features arise during evolution and its implications in neurological disorders. As an assistant professor, she lectures in human anatomy and embriology. As a scientist, she enjoys tackling questions involving nature vs nurture unsolved questions of developmental biology. In her lab, they try to solve them (at least partially) with the array of novel technologies that are currently available in their field, but also from others. Dr. Acosta believes all experimental models are equally valuable just depends on the question. So, running from any dogma, the ones her lab currently focuses on are those which she thinks will answer the questions they pose them. You've read the current questions tackled in their lab, but they have plenty more awaiting for younger scientists to be unveiled.

Josep M. Canals

Director of Creatio, production and validation center of Advanced Therapies, UBneuro, University of Barcelona, Spain.

Josep M. Canals is currently the director of Creatio, the Production and Validation Center for Advanced Therapies of the University of Barcelona. He has a PhD in neurobiology from the University of Barcelona, and he held a postdoctoral fellowship position at the Karolinska Institute in Stockholm where he began working on stem cells and Parkinson's disease. On his return to Barcelona Dr. Canals was awarded a Ramon y Cajal research position at the Institute of Biomedical Research August Pi i Sunyer (IDIBAPS). Two years later he was appointed associate professor at the Department of Cell Biology, Immunology and Neurosciences (now Biomedical Sciences) in the Faculty of Medicine and Health Sciences. Since then, his research laboratory of Stem Cell and Regenerative Medicine at the Department of Biomedical Sciences of the Faculty has focused on the use of stem cells as a therapy for neurodegenerative diseases, mainly focusing on Huntington's disease. and the principal investigator of the. His research group is integrated in the Spanish Network of Advanced Therapies. At the international level, Dr. Canals laboratory has managed to attract competitive private funding and be a part of a major collaborative effort led by the Cure for Huntington's Disease Initiative (CHDI. Nowadays, he is member of the steering committee of SC4HD, an international consortium for stem cell treatment of Huntington's disease. Between 2013 and 2017, he was invited expert at the European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO) of the European Directorate for the Quality of Medicines & Healthcare (EDQM) of the Council of Europe. Dr. Canals has published over 100 articles in internationally renowned outstanding journals, and he is currently coordinator of two European projects, he is also principal investigator of an American project, of four national public projects and of a private project of the La Caixa Foundation.

Nicolai Franzmeier

Junior Research Group Leader, Institute for Stroke and Dementia Research, Ludwig Maximilian of Munich University Hospital, Germany.

Dr. Franzmeier is an early career investigator with a strong focus on Alzheimer's disease neuroimaging research. He received undergraduate training in psychology and medicine from 2009-2014 in Innsbruck, Austria, after which he completed his PhD at the graduate school for systemic neurosciences (LMU) in Munich in 2017.
He is specifically interested in the spatiotemporal evolution of AD-related brain changes that underlie cognitive decline and those factors that provide resilience in AD. His overall goal is to develop clinically useful models for predicting disease progression and to identify therapeutically relevant targets for secondary prevention of AD dementia. To this end, he is combining structural & functional MRI with molecular PET imaging and genetics.

Additional resources:
isd-research.de/research-groups/franz-meier-lab/c2a419aceaa4aab7

Lluís Fuentemilla

Full Professor, Department of Cognition, Development and Educational Psychology, Faculty of Psychology, UBneuro, University of Barcelona, Spain.

Lluís Fuentemilla received the PhD in Psychology for his research on the neural mechanisms that support human sensory memory. He then moved to the Institute of Cognitive Neuroscience (University College London) to study as a postdoctoral researcher, a time that helped him crystallize his interest in understanding the brain underpinnings of human learning and memory. In 2010, he was awarded by a Ramon y Cajal programme to create and establish his own research group in Spain. In 2018 he was awarded with the ICREA Academia. Lluís Fuentemilla is now a Full Professor at the University of Barcelona (UB) where he leads the Dynamics of Memory Formation group. His research group is funded by several national and international funding agencies and industry.

His research group aims at understanding how the human brain supports the formation, the consolidation, and the retrieval of everyday life experiences. They use behavioural, neuroimaging and electrophysiological techniques that, combined with advanced analytical approaches, provide insights of the neural mechanisms that underlie fundamental memory processes, such as how experiences are integrated and transformed into long-term memory traces by the brain.

Raquel Sánchez-Valle

Head of the Neurology Service, Alzheimer's disease and other cognitive disorders group, Hospital Clínic de Barcelona, IDIBAPS, UBneuro, University of Barcelona, Spain.

Dr. Sánchez-Valle completed her training as a neurologist at the Hospital Clínic de Barcelona (2000) and her PhD degree on Biopathology in Medicine at the University of Barcelona (2003). After her PhD, she obtained a Rio Hortega fellowship (Instituto de Salud Carlos III, Spanish Ministry of Health) in Behavioural neurology at the Institut d'Investigacions Biomèdiques August Pi I Sunyer, Barcelona. During her fellowship, she accomplished a short-term postdoctoral scholarship at the Memory and Aging Center- University of California San Francisco, directed by Dr. Bruce Miller (2006). Back in Barcelona, she was hired as neurologist at the Alzheimer's Disease and other Cognitive Disorders (ADCD) unit, Hospital Clínic de Barcelona (2006-). In 2018, Dr. Sánchez-Valle became the Group Leader of the Alzheimer's disease and other cognitive disorders group at the IDIBAPS (https://www.clinicbarcelona.org/en/idibaps/research-areas/clinical-and-experimental-neuroscience/alzheimers-disease-and-other-cognitive-disorders) and Associate professor at the University of Barcelona. Currently, she is the Head of the Neurology Service at the Hospital Clínic de Barcelona.

Her research focuses on the use of different type of biomarkers (neuroimaging techniques, biochemical and genetic biomarkers) for the early and accurate diagnosis and prognosis/monitoring of neurodegenerative dementia, especially in early-onset and rare forms of dementia, as autosomal dominant Alzheimer's disease, frontotemporal dementia and prion diseases.

Total Pub (Pubmed): 251. Index H (WoS): 45.

Jesús Rodrigo

CEO of CEAFA (Spanish Confederation of Alzheimer), Spain.

CEO of Spanish Confederation of Alzheimer disease. Member of the board of Alzheimer's disease International (ADI). President of Alzheimer Iberoamerica (AIB). Former member of the board of Alzheimer Europe (until 2019). Member of the technical committee of the neurodegenerative diseases strategy of the National Health System. Member of the national dementia group devoted to the definition and elaboration of the national Alzheimer's plan 2019-2023. Participating in numerous projects and consultations, both at national and international level.

Christopher Guger

g.tec founder, Austria.

Christoph Guger studied electrical and biomedical engineering at the University of Technology Graz in Austria and Johns Hopkins University in the USA and received his PhD in 1999. In 1999, he started the company g.tec which has now branches in Austria, Spain, the USA, Canada, and Hong Kong. g.tec produces high-quality neurotechnology and real-time brain computer interfaces for the research, medical and consumer market. The company is active in many international research projects about brain-computer interfacing, neuromodulation, stroke rehabilitation, assessment and communication with patients with disorders of consciousness and high-gamma mapping in epilepsy and tumor patients.

Eduard Vieta

Full Professor of Psychiatry, UBneuro, University of Barcelona, Spain.

Eduard Vieta is full Professor of Psychiatry at the University of Barcelona, and Head of the Department of Psychiatry and Psychology at the Hospital Clínic, Barcelona, Spain, where he also leads the Bipolar and Depressive Disorders Program. His unit is one of the worldwide leaders in clinical care, teaching and research on affective disorders and precision psychiatry. He is also Scientific Director of the Spanish Research Network on Mental Health (CIBERSAM) and group leader at the Institute of Neuroscience.

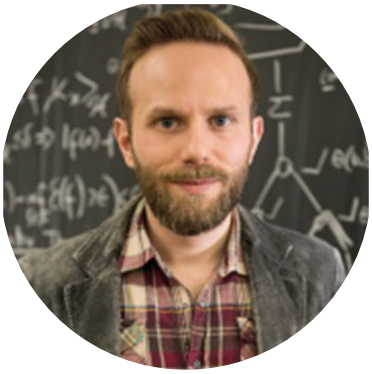
Professor Vieta has received various awards, including: the Aristotle Award, the Mogens Schou Award by the International Society of Bipolar Disorders, the Colvin Prize by the Brain & Behavior Foundation, the Clinical Neuroscience Lilly award by the International College of Neuropsychopharmacology, the Simon Bolivar Award by the American Psychiatric Association, the Excellence Award by the College of Physicians, the Trueta Award by the Medical Sciences Academy, and the Dissemination and Humanities Award by the University of Barcelona. He has been named best psychiatrist in Spain (Monitor Sanitario, El Español), is an honorary member of the Spanish Society of Biological Psychiatry and has also been awarded Doctor Honoris Causa by the University of Valencia. He is a member of the Royal Academy of Medicine of Catalonia.

Professor Vieta has authored more than 1,100 original articles, 500 book chapters and 50 books. His h-index is 145, he has over 80,000 citations and his papers have had over 700,000 downloads. He is the most cited author worldwide on bipolar disorder, has been listed as one of the "World's most influential minds" and is oin the Best Doctors list by Forbes. Furthermore, he is Editor-in-Chief of *European Neuropsychopharmacology*, has served as Invited Professor at McLean Hospital and Harvard University, Massachusetts, USA and as Neuroscience Scientific Advisor to the European Presidency.

Mel Slater

Distinguished Investigator, UBneuro, University of Barcelona, Spain.

Mel Slater is a Distinguished Investigator at the University of Barcelona, and co-Director of the Event Lab (Experimental Virtual Environments for Neuroscience and Technology). He was previously Professor of Virtual Environments at University College London in the Department of Computer Science. He has been involved in research in virtual reality since the early 1990s, and has been first supervisor of 40 students who achieved their PhDs in computer graphics and virtual reality since 1989. He was awarded the 2005 IEEE Virtual Reality Career Award: 'In Recognition of Pioneering Achievements in Theory and Applications of Virtual Reality'. He held an ERC Advanced Grant TRAVERSE 2009-2015 and has now a second Advanced Grant MoTIVE 2018-2023. He has also received two ERC Proof of Concept awards. He is currently Technical Leader of the European Horizon 2020 project GuestXR (2022-2025). He is Field Editor of Frontiers in Virtual Reality, and Chief Editor of the Human Behaviour in VR section. He has contributed towards bringing virtual reality into scientific endeavour, with publications in Nature Reviews Neuroscience, PNAS, Neuron, Cognition, and others. He has over 400 publications and h-index of 104 with 48930 citations (Google Scholar). He was awarded the Humboldt Research Prize from Germany in 2020. He is a co-founder of the spin-off company Virtual Bodyworks.



Xavier Boix

Research Scientist, Massachusetts Institute of Technology (MIT), USA.

Xavier Boix works as a research scientist at the Department of Brain and Cognitive Sciences at MIT (since 2021), leading a group investigating biologically-inspired machine learning. Xavier received a doctorate in machine learning from ETH Zurich (2014) and completed his postdoctoral training at MIT in the Sinha lab and also the Poggio lab, where he was part of the multidisciplinary Center for Brains, Minds and Machines. Xavier's research aims at developing a theory that facilities the next generation of learning machines by leveraging insights and tools from neuroscience. His research lives at the intersection of theoretical machine learning, engineering of deep neural networks, and neuroscience.

Diana Mihalache

UX Researcher, Google, USA.

Diana Mihalache is a UX researcher in Trust and Safety at Google. She focuses on the user experience of human reviewers in content moderation. Specifically, her work centers on wellness and cross-product metrics. Prior to her role at Google, she received a PhD in clinical psychology with a specialization in pediatric neuropsychology and developmental cognitive neuroscience.

Luis Montesano

Chief Scientific Officer at Bitbrain, Associate Professor (on leave), University of Zaragoza, Spain.

Dr. Luis Montesano received the Ph.D. degree in computer science and systems engineering in 2006, from the University of Zaragoza, Spain. He was a post-doctoral researcher at the IST, Lisbon from 2006 to 2009. He is currently Chief Scientific Officer at Bitbrain and is an Associate Professor (on leave) at the University of Zaragoza where he leads the bio-learning lab working in the areas of Brain-Machine Interfaces and cognitive systems. He has published over 80 international journal and conference papers in the main venues of robotics, AI and EEG based neurotechnology. He has participated in several national and European projects related to robot learning such as ROBOTCUB or HANDLE; language acquisition such as CONTACT; and neural engineering such as H2020-MOREGRASP, ITN-NETT, CONSOLIDER-HYPER or LAICO.

Ignasi Capellà

Co-founder of Broomx, Spain.

Sociologist graduated by the University of Barcelona, master in digital marketing and specialist in social innovation and European project management.
More than 15 years of experience in social innovation and project management in organizations such as Ajuntament de Sant Boi de Llobregat, DCB Tourism, Mobile World Capital Barcelona and ACCIÓ. Cofounder of Catalan immersive reality startup Broomx, he has lead the reorientation of the company to the healthcare and social care sector.

Carolina Aguilar

CEO, Co-founder, and Board Director, INBRAIN Neuroelectronics, Spain/Switzerland.

Business executive with corporate and startup experience. Unique blend between consumer goods and healthcare (medical devices) knowledge. More than 15 years of experience in European and Global positions managing complex environments from acquisitions to consolidated businesses with P&Ls up to $140 M all with high single to double digit growth % YOY. Inspirational, authentic with an in-depth business acumen. Specialized in deep tech, digital health technology, and business design with value-based healthcare principles for healthcare sustainability.

Ana Maiques

CEO & Co-Founder, Neuroelectrics, Spain.

Ana Maiques is the CEO of Neuroelectrics, a company aiming to change the way we interact with the brain, developing innovative technologies to monitor and stimulate the brain to help many patients in need. She was nominated by IESE Business School as one of the most influential entrepreneurs under 40 in Spain in 2010. She received the EU Prize for Women Innovators from the European Commission EC in 2014. In 2015 & 2016, she was named one of the most inspiring women on the Inspiring Fifty list in Europe. In 2022, together with 8 other spanish scaleups, she co-founder, EsTech, an organization of high-growth companies that want to make more visible the impact of a new productive model. Ana recently joined the European Innovation Council Advisory Board, the pan European organism that aims to scale up European companies. She continues breaking the barriers of science and technology in an impactful way with Business Ethics.

Andreu Oliver

Account Manager scientific research, Tobii, UK.

In the intersection between technical understanding and a business mindset, Andreu Oliver enjoys helping find the right market fit and interacting with all the stakeholders to understand how to match technology and research with the best chances of success. His primary role as an account manager is growth and exploring new opportunities and markets to capitalise on the products and the team. He has a PhD in Cognitive Psychology by training and have been working in neurotechnology in the academic and commercial sectors since 2015.

Rafael Yuste

Full Professor of Biological Sciences, Columbia University, USA.

Rafael Yuste, a neuroscientist, is Professor of Biological Sciences at Columbia University in New York. He studies the function and pathology of the cerebral cortex, using optical methods to measure and modify the activity of its neural circuits.

Yuste grew up in Madrid, Spain and obtained his M.D. at the Universidad Autónoma in Madrid. After working in Sydney Brenner's laboratory at the Medical Research Council in Cambridge, UK, he was a Ph.D. student with Larry Katz in Torsten Wiesel's laboratory at Rockefeller University in New York, and postdoctoral student of David Tank at Bell Laboratories in New Jersey. He joined Columbia in 1996 and since 2014 is director of its Neurotechnology Center.

In 2011 Yuste led a small group of researchers who proposed the Brain Activity Map, precursor to the US BRAIN Initiative, and in 2016 he helped coordinate the launch of an International BRAIN Initiative. In 2017, he also led the "Morningside" group of 25 researchers and clinicians who proposed novel human rights ("Neurorights") to protect citizens from potential abuses from neurotechnologies and AI.

Yuste's is a member of Spain's Royal Academies of Medicine and of Science and was a member of the Howard Hughes Medical Institute. His scientific contributions have been recognized by awards from the Mayor of New York City, the US Society for Neuroscience, the Director of the U.S. National Institutes of Health and the Cajal Institute. He shared the Eliasson Global Leadership Prize from the Tällberg Foundation in 2018 for his advocacy work.

For information about his research see:
https://blogs.cuit.columbia.edu/rmy5/
and for his advocacy work see:
https://neurorightsfoundation.org/

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Programme

WEDNESDAY, 9 NOVEMBER 2022

08:30 - 09:15	**Registration**
09:15 - 09:45	**Institutional welcome** Joan Guàrdia Olmos, Rector, UB Antoni Trilla, Dean, Faculty of Medicine and Health Science, UB Júlia Miralles de Imperial, Municipal policies of Science and Universities, Ajuntament de Barcelona Jordi Alberch, Director, Institute of Neurosciences, UB
09:45 - 10:45	**Opening plenary session** *Chair: David Bartrés, Brain health and neuromodulation group, UBneuro, UB, Spain* Michael Valenzuela, Centre for Healthy Brain Ageing, University of New South Wales, Australia, "Translation of neuroscience beyond academia"
10:45 - 11:15	**Coffee-break**

NEURODEVELOPMENT AND NEW TECHNOLOGIES SYMPOSIUM
Chair: Silvia Ginés, Mechanistic and therapeutic approaches in neurodegenerative disorders group, UBneuro, UB, Spain

11:15 - 11:55	*Invited speaker.* Míriam Pérez Cruz, BCNatal | Fetal Medicine Research Center; Institut de Recerca Sant Joan de Déu; RICORS group. Barcelona, Spain, "Neurosonography and brain electrophysiology in fetal neurodevelopment"
11:55 - 12:15	Sandra Acosta, Neurodevelopmental disorders group, UBneuro, UB, Spain, "Brain organoid models of neurodevelopmental disorders powered up by deep learning"
12:15 - 12:35	Josep Maria Canals, Stem cells and neurodevelopment group, UBneuro, UB, Spain, "In silico and in vitro modeling of human neurodegeneration"

Flash talks

12:35 - 12:45	Yasmina Manso, Developmental neurobiology and regeneration group, UBneuro, UB, Spain, "Spatial and cell-specific contribution of Reelin expressed by Cajal-Retzius cells or GABAergic interneurons to cortical lamination"
12:45 - 12:55	Natàlia Gorina-Careta, Brainlab group, UBneuro, UB, Sant Joan de Déu Research Institute, Spain, "Effects of a bilingual fetal acoustic environment on the neural sound encoding of newborns"
12:55 – 13:05	Anna-Christina Häb, Neural stem cells and brain damage group, UBneuro, UB, Spain, "Human iPSC-derived neurons allow dynamic monitorization of complex network activity for machine learning"

WEDNESDAY, 9 NOVEMBER 2022

13:05 - 15:00 **Lunch / Poster session**

AGING IN HEALTHY AND PATHOLOGICAL BRAIN SYMPOSIUM
Chair: Mercè Pallàs, Neuropharmacology in ageing and Alzheimer's disease group, UBneuro, UB, Spain

15:00 - 15:40 *Invited speaker.* Nicolai Franzmeier, Institute for Stroke and Dementia Research, Ludwig Maximilian of Munich University Hospital, Germany, "Using multimodal neuroimaging to understand Alzheimer's disease progression"

15:40 - 16:00 Lluís Fuentemilla, Brain plasticity and connectivity: language, memory and reward group, UBneuro, UB, Spain, "Rapid memory formation, consolidation, and transformation"

16:00 - 16:20 Raquel Sánchez-Valle, Clinical research in Alzheimer's disease and other cognitive disorders group, UBneuro, UB, Spain, "Catching a glimpse of Alzheimer's disease brains"

16:20 - 16:40 Jesús Rodrigo, CEAFA-Confederación Española de Alzheimer, Spain, "Pathological brain. Is only about aging?"

Flash talks

16:40 - 16:50 Kilian Abellaneda, Brain health and neuromodulation group, UBneuro, UB, Spain, "Purpose in life: a psychological factor promoting cognitive resilience and neuroprotection"

16:50 - 17:00 Julia Solana, Mechanistic and therapeutic approaches in neurodegenerative disorders group, UBneuro, UB, Spain, "Neuron-derived EVs modulate synaptic plasticity"

17:00 - 17:10 Álvaro González, Addiction and dual disorders group, UBneuro, UB, Spain, "Cognitive performance in patients with dual disorders: the influence of the type of severe mental illness"

17:10 - 19:00 **Cocktail reception**

THURSDAY, 10 NOVEMBER 2022

08:30 - 09:00 **Registration**

NEUROTECHNOLOGIES AND BRAIN DISORDERS SYMPOSIUM
Chair: David Bartrés, Brain health and neuromodulation group, UBneuro, UB, Spain

09:00 - 09:40 *Invited speaker.* Christoph Guger, Neurotechnology and real-time brain computer interfaces, g.tec, Austria, "Current and future applications of brain-computer interfaces"
09:40 - 10:00 Eduard Vieta, Bipolar disorders group, UBneuro, UB, Spain, "Digital innovation in mental health"
10:00 - 10:20 Mel Slater, Virtual reality group, UBneuro, UB, Spain, "Vicarious Agency in Virtual Reality"

Plenary session on Neurotechnologies
Chair: Petia Radeva, Artificial intelligence group, UBneuro, UB, Spain

10:20 - 11:00 *Invited speaker.* Xavier Boix, Brain and cognitive science department and Sinha Lab for developmental research, MIT, USA, "The neuroscience of learning machines"

11:00 - 11:30 **Coffee-break**

Neurotechnologies TED Talks
Chair: Petia Radeva, Artificial intelligence group, UBneuro, UB, Spain

11:30 - 12:00 *Invited speaker.* Diana Mihalache, Trust and safety group, Google, USA, "Human Reviewer Experience: Wellness in the Context of Content Moderation "
12:00 - 12:15 Luis Montesano, Bit Brain, Spain, "Bringing neurotech home for neuro-rehabilitation"
12:15 - 12:30 Ignasi Capellà, Broomx, Spain, "Immersive technologies: an effective tool for neurorehabilitation?"
12:30 - 12:45 Carolina Aguilar, INBRAIN Neuroelectronics, Spain-Switzerland, "Neurotechnology… What's next?"
12:45 - 13:00 Ana Maiques, Neuroelectrics, Spain, "Will a digital copy of your brain help personalize therapies in patients suffering from brain disease? The future is here: Neurotwin"
13:00 - 13:15 Andreu Oliver, Tobii, UK, "The transition from research to day-to-day practice and how companies can help with the process"

13:15 - 13:45 **Discussion:** How technology can improve our knowledge of the brain

THURSDAY, 10 NOVEMBER 2022

13:45 - 15:45	**Lunch / Poster session**
Flash talks	
15:45 - 15:55	Mariarca Ascione, Virtual reality group, UBneuro, UB, Spain, "A single session of an attentional bias modification task based on virtual reality and eye-tracking to reduce attentional bias and body dissatisfaction in anorexia nervosa"
15:55 - 16:05	Franck-Alexandre Meschberger-Annweiler, Virtual reality group, UBneuro, UB, Spain, "Attentional bias modification, through Virtual Reality-based body exposure, to enhance efficacy of treatment of anorexia nervosa"
16:05 - 16:15	José Valenzuela, Brainlab group, UBneuro, UB, Spain, "A Convolutional Neural Network approach for auditory stimuli classification from the frequency following response"
16:15 - 17:00	**Closure plenary session** *Chair: Jordi Alberch, Neuronal network dysfunction in neurological and psychiatric disorders group, UBneuro, UB, Spain* *Invited speaker.* Rafael Yuste, Neurotechnology Center, Columbia University, USA, "Neurotechnology: An upcoming revolution in science, medicine and society"
17:00 – 17:20	**Flash talk and poster Awards**
17:20 - 17:30	**Closing event:** **Future directions of scientific work and conclusions** Silvia Ginés, Congress Chair Jordi Alberch, UBneuro Director

Abstracts

Translation of neuroscience beyond academia

Michael Valenzuela
Centre for Healthy Brain Ageing, University of New South Wales, Australia

Translation is defined formally by Merriam Webster in three ways: a) rendering from one language into another; b) alteration to a different substance, form, or appearance, and c) transformation of coordinates in which the new axes are parallel to the old ones.

Each definition is interesting and characterised by movement, energy, and beyond anything, change. In this presentation, I have been given the special opportunity to consider each sense with respect to my career thus far in neuroscience.

Perhaps the textbook form of translation involves rendering from the language of science to natural language. This is a fine skill but not necessarily well taught in academia.

Early on in my career, I happened to write the book Maintain Your Brain as a way of capturing the state of the art of dementia prevention at the time, in easy digestible language. It was far more popular than expected and led to the creation of BrainyApp, the world's first evidence-based brain health smartphone app. Book sales and App downloads combined are in the 100,000s – evidently the public are hungry for this material, but my academic colleagues were lukewarm on the idea. Critical to the art of translation is the notion of credibility and expertise, values academics frequently under appreciate.

Transmutation of substance is what I am most intensely engaged in at the moment. In university, my research lab discovered a method of growing neuronal precursors from the human hair follicle, and perhaps our greatest ambition was to publish a high impact paper, or apply for a six-figure grant. Purely by chance, I met and became friends with an expert entrepreneur, and he convinced me to create a company to take this forward to human trial.

Funding in the world of biotech venture capital is no less competitive than in academia, but the quanta are orders of magnitude higher. Yet successful translation in this arena requires intellectual property to undertake a series of transformations, each outside of the academic comfort zone. These include protection, valorization, commodification, industrialization and, deu meu, monetization. What the process has taught me is how under-prepared academics are not only to commercialize their inventions, but even how to think about it.

Critical to this type of translation is crystal clarity of mission, bringing together a power-projecting team, cultivating trust-based partnerships, investing sufficient time on planning, and above all, ensuring that interests are aligned.

Finally, translation as movement to a new place whilst conserving key inter-relationships, is where the Maintain Your Brain Trial (MYB) is at the moment. MYB is the world's largest dementia prevention trial (N=6236) and recently returned positive primary outcomes at the three-year follow up stage, including a more than one-year delay in cognitive decline. The size and scope of MYB has also led to some fascinating insights, such as a vocal biomarker of cognitive reserve – a construct of interest across my career and now seen in a new light by virtue of different machine learning analyses.

A translational arc will be traced from MYB's origins in observational studies, then small clinical trials, then online development. But more significant is the question of how to make the next and ultimate translation: how to deliver MYB to every accessible older person globally? To achieve this every sense of translation will have to be marshalled, including collaboration with international public health institutions and leveraging the distribution power of mass consumer digital devices.

Neurosonography and brain electrophysiology in fetal neurodevelopment

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It is estimated that 10% of newborns will have some neurodevelopmental disorder during the future life and that 2/3 of these have their origin in prenatal life. Foetal conditions such as intrauterine growth restriction, pre-eclampsia, monochorionic gestation, congenital heart disease, among others, are associated with neurodevelopmental disorders during childhood, adolescence and adulthood. In recent years, a increasing number of studies have focused on the study of the foetal brain in order to isolate neuroimaging biomarkers that may be useful in identifying foetuses at increased risk of neurodevelopmental disorders. Neurosonography is the multiplanar study of brain structures using ultrasound and allows detailed assessment of the growth and maturation of these structures. This technique has identified changes in brain circulation, size and cortical maturation in at-risk populations, some of which have been correlated with postnatal neurodevelopment. One of the most prevalent neurodevelopmental disorders is language development disorder, which has a prevalence of around 8% in kindergarten. It is considered a public health problem associated with an increased risk of school failure, poor employment outcomes, and social, emotional and behavioural problems. However, there are few tools to early diagnose future language impairment in order to implement measures to improve the prognosis of these children. Among them, the frequency-following response (FFR) is a non-invasive electrophysiological measure that reflects the neural encoding of the temporal and spectral characteristics of complex sounds in the auditory hierarchy. Alterations in FFR are found in children with deficits in phonological awareness, reading and abnormal temporal resolution. In addition, neurodevelopmental disorders characterised by impaired communication and literacy skills, such as dyslexia or autism spectrum disorder (ASD), have been associated with abnormal subcortical representation of speech sounds. FFR is a useful tool to anticipate children with reading and literacy impairments that could benefit of early preventive measures to improve the neurological prognosis in this area. My talk will discuss our current efforts in the study of prenatal biomarkers of neurodevelopment, the study of neural transcription of speech sounds by FFR in newborns to understand the early maturation of complex sound processing and its correlation with foetal brain structures as a way to detect and improve neurodevelopment in at risk population.

Brain organoid models of neurodevelopmental disorders powered up by deep learning

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Brain organoids are self-assembled in vitro 3D cell structures that recapitulate human brain development. In the last decade, brain organoids have risen as a powerful tool to study neurological disorders, including brain tumors and neurodevelopmental pathologies.

However, brain organoids are intrinsically highly morphologically variable structures, thus limiting its use for obtaining reliable predictions of their phenotype and harnessing their scalability. Moreover, their analysis depends on highly trained human expertise and sophisticated technologies at end-point. Deep learning (DL) has reached human level performance for many so far machine-learning unsolvable problems. Here we describe a DL approach to classify organoids upon a genetically driven neurodevelopmental disorder, such as Dravet Syndrome (DS). DS is a genetic epileptic encephalopathy with an early infancy onset driven by mutations in the sodium channel subunit gene SCN1A. Our multistep DL approach, herein named Image Phenotyping Network (ImPhenet), consists in the normalization of the microscopy live images followed by a predictive DL model to classify the organoids into healthy and DS. The ImPhenet framework shows a high performance in the classification of control and DS organoids and can eventually be used as a model to determine the effect of drug on DS organoids. Altogether, we provide a proof-of-concept of the use of DL to determine the phenotype of neurodevelopmental disorder brain organoids and their implementation as a drug testing method.

In silico and *in vitro* modeling of human neurodegeneration

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Biomedical research and scientific authorities are currently placing rising pressure to Reduce, Refine and Replace (3R) the use of animals for research, data production and validation processes.

In order to improve the ethical landscape of preclinical research while maintaining the quality of scientific data, new technologies are required to model and decipher physiologic and pathologic mechanisms of neurodegenerative disorders. In silico and in vitro alternative systems have evolved over years and are in continuous development since they allow quick and high throughput drug screening to investigate the efficacy and toxicology of different compounds, before moving to in vivo application.

In this context, we set-up a new platform - Avantdrug® - to generate reliable alternative human-related models using neurons derived from human pluripotent stem cells (hPSCs). Our platform also integrates multiple interacting hPSC-derived neurons in a brain-on-chip system, improving the pertinence and validity of drug screening or toxicity assays in reproducible neuronal networks. To generate our in vitro models, we established robust protocols to culture and differentiate hPSCs into mature neurons under high-quality standard operating procedures (SOP), complying with the guidelines set by the UNE-EN-ISO 9001.

To develop in silico models of human neurodevelopment, we integrate high-throughput data sets from Single Cell RNAseq and bulk RNAseq, Calcium imaging and spatial transcriptomics using artificial intelligence. These models allowed us to model the trajectories of human neurodevelopment and their affections in neurodegerenative disorders. Using our in silico aproach, we can also predict how changes in gene expression may revert the pathological affections.

The prospect of recreating human neuronal connections to test toxins and drugs with no need for animal use is very promising and represents the new generation of models that are pushing forward pharmacologic research for humans.

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Spatial and cell-specific contribution of Reelin expressed by Cajal-Retzius cells or GABAergic interneurons to cortical lamination

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The extracellular protein Reelin, expressed by Cajal-Retzius (CR) cells at early stages of cortical development and at late stages by GABAergic interneurons, regulates radial migration and the "inside-out" pattern of positioning. Current models of Reelin functions in corticogenesis focus on early CR cell-derived Reelin in layer I. However, developmental disorders linked to Reelin deficits, such as Schizophrenia and Autism, are related to GABAergic interneuron-derived Reelin, although its role in migration has yet to be established. Using conditional transgenic mouse models, we selectively inactivated the Reln gene in CR cells or GABAergic interneurons and analyzed cortical lamination at different developmental stages using layer-specific markers, BrdU-birthdating, electroporation and progenitor cell transplant experimental approaches. We show that CR cells have a major role in the inside-out order of migration, while CR and GABAergic cells sequentially cooperate to prevent invasion of cortical neurons into layer I. Furthermore, GABAergic cell-derived Reelin compensates some features of the reeler phenotype and is needed for the fine-tuning of the layer-specific distribution of cortical neurons. In the hippocampus, the inactivation of Reelin in CR cells causes dramatic alterations in the dentate gyrus and mild defects in the hippocampus proper. These findings lead to the proposal of a novel model of Reelin action based on the spatial and cell-specific expression of this key protein in which both CR and GABAergic cell-derived Reelin cooperate to build the inside-out order of corticogenesis. Because several neuropsychiatric disorders are linked to Reelin deficits in interneurons, this study may provide a better understanding of the mechanisms associated to human brain disorders linked to abnormal migration and Reelin deficits.

Effects of a bilingual fetal acoustic environment on the neural sound encoding of newborns

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Language experience shapes how the auditory system processes sounds from the first moments in life. Early childhood is the developmental window when learning has a maximal influence on neural function and learning a second language in early childhood is a driving factor of functional neuroplasticity. Even though the auditory system of newborns is not biased to the native language of their parents, exposure to specific language environment alters infants' speech perception during the first year of life. Yet, several studies have demonstrated that even fetal hearing experiences shape the infants' musical and linguistic preferences. As bilingualism, relative to a monolingual environment, has been demonstrated to enhance evoked responses to speech in children and adults, the present study sought to determine whether a bilingual environment during pregnancy modulates the newborn's ability to processing sounds. To do so, the frequency-following response (FFR), an auditory evoked potential elicited to complex sounds, was recorded in a sample of 90 healthy term neonates during their first days of life. Newborns were divided into two groups according to their prenatal language exposure as reported by their mothers through a questionnaire (45 exposed to a bilingual fetal acoustic environment; 41 monolingual-exposed). The FFR was recorded to an /oa/ stimulus and quantified as the spectral amplitude and signal-to-noise ratio (SNR) at the stimulus F0. Results revealed that neonates exposed to a monolingual environment exhibited larger SNR of the F0 as compared to the bilingual group, whilst no differences where observed on the spectral amplitude of the F0. These results suggest that prenatal language exposure modulates the neural responses to human speech at birth and, in particular, we observe that a fetal monolingual environment provides a more stable background for newborns to encode and process sounds. Our results contribute to the current hypothesis that bilingual infants commence the process of language acquisition by separating languages from birth by demonstrating that, whilst a monolingual fetal environment provides a more stable background, bilingually exposed newborn's auditory system is tracking a wider range of frequencies.

Human iPSC-derived neurons allow dynamic monitorization of complex network activity for machine learning

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Modern world is increasingly dependent upon artificial intelligence and machine learning. Applications range from decision making in areas such as health and finance up to autonomous vehicle control. However, current deep-learning machines and neural network algorithms have important limitations, namely ineffective learning rules, long training, and high-power consumption (1). In the present project, we aim to address these limitations by using the human nervous system itself as a model, which can process external information in a power-efficient way. By using stem cell technology, we generate human neural networks that integrate human iPSC-derived neurons and glial cells. These cultures, grown on a special multielectrode arrays (MEAs) chip and forming predesigned conformations (2), will dictate their neuronal connectivity during network maturation using physical and chemical cues. The MEAs setup allows for high-resolution recordings of neuronal activity in combination with precise bidirectional microelectrode stimulation of specific cells. This enables the training of the neuronal cultures to achieve a particular response. Parameters that govern neuronal circuits response to patterned stimuli can be determined and analyzed in the context of information theory, paving the way towards trainable circuits with desired processing capabilities. Obtained data will provide detailed information about the complex network dynamics between large populations of human neurons, which will lead to the development of new tools for medical image diagnoses, biosensing or monitoring. Using these biological learning rules and powerful human-brain-based circuits, the present project falls into novel and widespread advances in machine learning abilities and beyond, leading to a paradigm-shift in artificial intelligence technology and applications.

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Using multimodal neuroimaging to understand Alzheimer's disease progression

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Alzheimer's disease (AD) is a progressive neurodegenerative disease that is characterized by the cerebral accumulation of fibrillary amyloid and tau pathology, which together lead to neurodegeneration and cognitive decline. Thus, it is critical to understand the pathophysiological mechanisms of AD progression to identify potential treatment targets for i) attenuating amyloid and tau accumulation and ii) therefore neurodegeneration and cognitive decline. In this presentation, I will summarize some of our key past research efforts to better characterize pathobiological and clinical AD progression by embedding multimodal neuroimaging and biomarkers in a hypothesis-driven mechanistic framework. The first part of the presentation will cover how activation of the brains innate immune cells (i.e. microglia) may be protective against the development of amyloid plaque pathology and downstream cognitive decline in AD patients and those at genetic risk of AD. The second part will cover mechanisms that facilitate the amyloid-related development and spreading of tau pathology in AD, i.e. the key driver of neurodegeneration and cognitive decline. Specifically, I will outline how tau pathology develops in circumscribed brain regions in AD patients from where it spreads throughout connected brain regions, suggesting that brain networks are key roadmaps for the trans-neuronal spreading of tau pathology in AD. Further, I will show that genetics and inter-individual differences in brain network architecture can influence the accumulation rate and spreading pattern of tau pathology. In the third part of the presentation, I will emphasize that amyloid and tau pathology do not exert the same impact on cognitive performance in each individual, but that a subpopulation of AD patients can show remarkable resilience against developing dementia symptoms. Here, I will summarize our previous work, suggesting again that a more efficient topology of brain networks may play an important role in facilitating resilience against cognitive decline in AD patients. Overall, this presentation will provide an overview of how we can use multimodal imaging (i.e. PET and MRI) as well as fluid biomarkers to better understand the cascade of pathologies in AD.

Rapid memory formation, consolidation, and transformation

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Like other systems in nature, memories evolve to adapt to the ever-changing environment, increasing their chance of persistence over time. During this process though, original memory representations are subjected to neural mechanisms that may transform them, bringing opportunities for memory strengthening, modification, and even forgetting. In this talk, I will outline emergent findings on healthy population and neurological patients emphasizing the role of memory reactivation as a brain mechanism to promote memory formation and transformation during awake and during sleep. The talk will also document existing methods that can automatically track individual and real-life autobiographical memories that may inspire novel interventional techniques to ameliorate memory disturbances associated to neurodegenerative diseases.

Catching a glimpse of Alzheimer's disease brains

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In 1906, Dr. Alois Alzheimer described a new clinicopathological entity that was later called after him, Alzheimer's disease. Until 2011, the clinical diagnosis of Alzheimer's disease in living individuals was based only clinical features, but the certainty of the diagnosis was limited, and clinicopathological series disclosed 25% of misdiagnosis. Biotechnological innovation and advances in the knowledge of the disease provided the opportunity to identify biomarkers that might mirror neuropathological findings with the aim to support and improve the clinical diagnosis. In the earlier 90s of the XX century, the increase of total tau levels and the decrease of Ab42 levels in cerebrospinal fluid were first proposed as biomarkers of Alzheimer's disease. After several decades of clinical research, these markers, in addition to increased levels of phospho-tau were included in the clinical criteria and now are part of the clinical work-up in most Tertiary centers, especially, in early phases of the disease or atypical cases. The development of tracers that bind to amyloid plaques, first, and more recently to tau deposits, and can be quantified using Tomography emission positron scans in patients improved the diagnosis and, has been a relevant step forward for the study of the evolution of the pathological deposits in the brain along the disease process. More recently, several biochemical markers, associated to amyloid deposition (p-tau spices), neurodegeneration (neurofilament light) and neuroinflammation (GFAP) measurable in blood samples have been identified and are being investigated in clinical cohorts. Clinical symptoms remain the core of the disease and the disease diagnosis, but we are able now to glimpse Alzheimer's disease brains as only neuropathologists could, for clinical and research purposes. These biomarkers also provide the opportunity now to evaluate the target engagement of drugs directed against amyloid or p-tau or the effect of these drugs in the neurodegenerative process. However, the classical underling neuropathological changes do not explain all the features of the clinical disease and are state markers: they are not useful, at this point, for example, for establishing a prognosis. In summary, we will present a state-of-the-art review about biomarkers for the Alzheimer's disease neuropathological process identification in living individuals.

Pathological brain. Is only about aging?

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CEAFA – Confederación Española de Alzheimer (Spanish Alzheimer's Confederation)

A diseased brain gives rise to different types of pathologies well identified by medical science, highlighting Dementias and, in particular, Alzheimer's. The brain is an organ that, like the person, ages and, consequently, progressively loses abilities and functions that affect people's daily lives.

Dementias are associated with age; about 90% of cases are diagnosed in older people and, many times, in advanced stages of the disease. However, and according to the World Health Organization, more than 9% of cases have been diagnosed in young people under the age of 65 and in early stages of evolution or onset of dementia.

Traditionally, attention has been directed towards the people who make up that 90% of cases. However, and thanks to scientific advances that, among other things, are allowing access to early diagnosis, it is foreseeable that young people will increase their number in the short-medium term. They are people who present new interests and needs that must be detected and understood and who, despite having a damaged brain, still retain a good part of their abilities.

From here, three key ideas must be emphasized.

The first, to promote research, scientific studies to diagnose early, even in prodromal phases, including the participation in trials of these people. Despite the reluctance of some professionals, from the point of view of the affected family the sooner the diagnosis or the probability of developing Alzheimer's in the future is of high importance, since it will allow them to assimilate the future that lies ahead, make decisions, plan the future, etc.

The second idea focuses on detecting and understanding the needs and interests of these new groups of people who cannot be incorporated into programs based on non-pharmacological therapies more focused on people with more advanced dementia. In this sense, it can be cited, for example, the Expert Panel of People with Alzheimer's, the PEPA, promoted by CEAFA since 2017 following the experience of other countries. This panel, which is not a therapeutic group, allows people not to talk about their disease, but about the experience lived in relation to it, as a previous step to propose solutions or proposals to improve this experience both their own and that of those who may suffer from dementia in the future.

The third idea is to ensure that these people are not excluded from their closest social environments, favoring that they can continue to contribute to Society, in a very similar way to how they were doing before the diagnosis.

Purpose in life: a psychological factor promoting cognitive resilience and neuroprotection

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Background: Disease-modifying agents to counteract cognitive impairment in older age remain elusive. Hence, identifying modifiable factors promoting brain reserve and resilience is paramount. In Alzheimer's disease (AD), education and occupation are typical reserve proxies. However, the importance of psychological factors is being increasingly recognized, as their operating biological mechanisms are elucidated. Purpose in life (PiL), one of the pillars of psychological well-being, has previously been found to reduce the deleterious effects of AD-related pathological changes on cognition. However, whether PiL operates as a cognitive resilience factor in middle-aged individuals, and what are the underlying neural mechanisms remains unknown.

Methods: Data was obtained from 624 middle-aged adults (mean age 53.71±6.9; 303 women) from the Barcelona Brain Health Initiative cohort. Individuals with lower (LP; N=146) and higher (HP; N=100) PiL rates, according to the division of this variable into quintiles, were compared in terms of cognitive status, a measure reflecting brain burden (white matter lesions; WMLs), and resting-state functional connectivity (rs-FC), examining system segregation (SyS) parameters using 14 common brain circuits.

Results: Neuropsychological status and WMLs burden did not differ between PiL groups. However, in the LP group greater WMLs entailed a negative impact on executive functions. Subjects in the HP group showed lower SyS of the dorsal DMN (dDMN), indicating lesser segregation of this network from other brain circuits. Specifically, HP individuals had greater inter-network connectivity between specific dDMN nodes, including the frontal cortex, the hippocampal formation, the midcingulate region, and the rest of the brain. Greater functional connectivity in some of these nodes positively correlated with cognitive performance.

Conclusion: Expanding previous findings on AD pathology and advanced age, present results suggest that higher rates of PiL may promote cognitive resilience already in middle age. Furthermore, having a purposeful life implies greater functional integration between the dDMN and other brain areas, which may represent a neuroprotection mechanism associated with better cognitive function.

Neuron-derived EVs modulate synaptic plasticity

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Neurodegenerative diseases induce an impairment in synaptic plasticity which eventually leads to cognitive symptoms in patients. Extracellular vesicles, which are involved in intercellular communication, have been suggested to be involved in synaptic processes, as they are carriers of bioactive miRNAs, proteins and lipids that can influence firing rate in recipient neurons. The aim of this study is to investigate whether neuronal EVs have a direct role in the regulation of synaptic plasticity.

Extracellular vesicles (EVs) were isolated from rat cortical neurons culture media, by ultracentrifugation, and used to treat sister cultures for 24h. Samples were subjected to immunohistochemistry, Western blotting and calcium imaging analysis.

We described that EVs are taken up by neurons both in the soma and in dendrites, and even in synaptic spines. We found that neuronal EVs carry synaptic proteins and enhance the consolidation of glutamatergic synapses in recipient neurons. We also observed a mild effect of EVs over neural network dynamics. Moreover, EVs had a trophic effect in neurons under nutrient deprivation conditions.

All these data put neuronal EVs in the spotlight to understand synaptic plasticity impairment in neurodegenerative conditions and use them as a possible therapeutic approach.

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Cognitive performance in patients with dual disorders: the influence of the type of severe mental illness

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Background: The coexistence of a substance use disorders (SUD) and a severe mental illness in the same patient is highly prevalent and it is associated with cognitive deficits in the patient's performance. The most common comorbid diagnoses to SUD in clinical samples are schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD). Since this comorbidity, called dual disorder, has its own clinical and neurocognitive features the present study explores the cognitive performance of a sample of patients with SUD and comorbid SZ, BD or MDD.

Materials and methods: 120 under treatment male patients with SUD were divided into three groups depending on their comorbid SMI diagnosis (SZ n=40, BD n=40, and MDD n=40) and assessed with a neuropsychological battery of tests for measuring attention, vocabulary, verbal learning, memory, processing speed, and cognitive flexibility. MANOVA analyses were carried out to explore the characteristics of each group and their possible differences. Additionally, a global performance Z score considering all the tasks was calculated for each group according to normative data.

Results: There were no significant differences among groups in vocabulary, processing speed, and cognitive flexibility. On the other hand, patients with SZ presented the worst performance in short term memory, verbal learning, attention, and recognition ($F(2,119) \geq 4.421$; $p \leq 0.014$; $p\ 2 \geq 0.070$). The analysis of the verbal learning curve for patients with SZ showed that they perform worse as the test progresses without having the beneficial effect of word repetition, and this pattern of execution was not found in patients with either BD or MDD. Patients with BD and MDD showed a very similar cognitive performance with no differences between them in the majority of the tasks. Moreover, when compared to normative data all patients of our sample presented difficulties in verbal learning, short-term memory, and recognition. The global performance Z score considering the execution in all the tasks evidenced an impaired cognitive pattern of performance for patients with SZ while the execution of the tasks was close to norms for patients with BD and MDD (which presented a similar performance).

Conclusions: Our research showed that the cognitive performance of patients with SUD and a comorbid severe mental illness depends on the type of psychiatric diagnosis. In this sense, patients with SUD and comorbid SZ presented more difficulties than those with BD or MDD. SZ diagnosis was linked with short term memory problems and no beneficial effect in verbal learning with word repetition. While future research should explore thoroughly the possible role of these difficulties as indicators or endophenotypes for dual schizophrenia spectrum disorders, prevention and intervention strategies could consider working to improve such limitations.

Current and future applications of brain-computer interfaces

Christoph Guger

Neurotechnology and real-time brain computer interfaces, g.tec, Austria

Brain-Computer Interfaces are used for many different applications with invasive and non-invasive sensors. These systems are successfully used for the rehabilitation of stroke patients, the assessment of command following in patients with disorders of consciousness or in neurosurgery to find the most important centers of the brain within minutes.

Digital innovation in mental health

Eduard Vieta

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The constant growth and widespread availability of digital technologies (i.e. smartphones and wearables) over the last decades have been a subject of intense interest and research in psychiatry. The potential of digital tools at collecting a new kind of passive and active information while providing cost-effective and tailored interventions have raised many hopes. In this session, we will briefly review the latest evidence-based advancements in the field of psychiatry using digital technologies, particularly in mood disorders. Among them we will present at least 3 projects of our group using digital tools. Challenges in the academic field hampering the advancement of these technologies and its implementation into clinical practice will be discussed.

Vicarious Agency in Virtual Reality

Mel Slater
Event Lab, Virtual Reality group, UBneuro, UB, Spain.

In virtual reality (VR) we perceive a computer generated sensory stream through a wide field-of-view, head-tracked, stereo head-mounted display (HMD). Wherever we look we perceive the virtual environment rather than the physical world. Ideally the same applies to other senses. In particular if we look down towards our body we see a life-sized virtual body coincidence in space with our real body. Through tracking, the virtual body moves synchronously and correspondingly with our real body movements. This typically gives rise to the illusion of body ownership over the virtual body. Given this ownership, suppose the virtual body carries out an independent act. Under particular conditions we may have agency over that action even though we did not initiate it ourselves. This is referred to as illusory or vicarious agency. In this talk I will describe an experimental study that shows that when participants have body ownership over their virtual body, and the virtual body spontaneously speaks then participants can have the sense of agency over the speaking, and it can also influence how they speak later after the exposure (1). This finding has implications for the forward model of agency (2). A further experimental study embodied participants in a robot through which they spoke to a confederate (3). Under conditions of body ownership over the robot body, participants felt responsibility and apologized for insulting words that the robot itself interjected in the conversation. I will discuss the implications of these findings for the forward model of agency. Finally I will describe an application of vicarious agency that helps diminish paranoia amongst people who suffer from persecutory ideation (4).

1. Banakou D & Slater M (2014) Body Ownership Causes Illusory Self-Attribution of Speaking and Influences Subsequent Real Speaking. PNAS 111(49):17678-17683.

2. Haggard P & Chambon V (2012) Sense of agency. Current biology : CB 22:R390-392.

3. Aymerich-Franch L, Kishore S, & Slater M (2019) When your Robot Avatar Misbehaves you are Likely to Apologize: an exploration of guilt during robot embodiment. International Journal of Social Robotics 12:217–226.

4. Gorisse G, Senel G, Banakou D, Beacco A, Oliva R, Freeman D, & Slater M (2021) Self-observation of a virtual body-double engaged in social interaction reduces persecutory thoughts. Scientific reports 11(1):1-13.

The neuroscience of learning machines

Xavier Boix
Brain and cognitive science department and Sinha Lab for developmental research, MIT, USA

Deep Neural Networks (DNNs) are fueling a new technological revolution based on intelligence. An important limitation of DNNs is that we currently are largely ignorant of their learned mechanisms, and understanding these mechanisms is necessary for the reliability, safety, and fairness of DNN-based technologies. I will present an approach to understanding DNNs that borrows insights and tools from neuroscience, as it articulates hypotheses and tests them as if DNNs were another brain. The talk will review our recent progress to understand the generalization capabilities of DNNs and address bias by leveraging insights from neuroscience about the mechanisms at the individual neuron level.

Human Reviewer Experience: Wellness in the Context of Content Moderation

Diana Mihalache
UX, Trust and Safety, Google, USA

As the amount for user-generated content increases, so does the need for human reviewers to moderate this content in order to protect the public. There are an estimated 100,000 human reviewers in commercial content moderation across large technology companies (Steiger, 2021). Their work is challenging and yet frequently overlooked. It can involve repetitiveness, high decision complexity, and/or exposure to graphic content—all of which can have an impact on wellbeing. Commercial content moderation is a relatively young field. The short term and long term impact of doing such work— as well as how to best protect the wellbeing of these reviewers—are not yet fully understood. At Google, we are tackling these challenges through research, design, and development of best practices.

Bringing neurotech home for neuro-rehabilitation

Luis Montesano
Bit Brain, Spain

Bitbrain is a spin-off of the University of Zaragoza that aims to bring neurotechnology closer to users, allowing its use in a simple way in an ecological context. During the talk we will address neuro-rehabilitation of stroke patients using brain-computer interfaces, focusing on how to transition the technology from the laboratory to the user's home. In particular, we will present preliminary results for upper limb rehabilitation carried out in a European project in collaboration with the Tubingen Hospital and PromotionSoftware.

Immersive technologies: an effective tool for neurorehabilitation?

Ignasi Capellà
Broomx, Spain

The era of digitalization and technological innovation we're living brings health professionals, scientific investigators and society in general with new tools that were unimaginable a few years ago, or only available to a very few organizations. Immersive technologies are one of these key innovations, and they have become very popular in recent years due to huge investments from global corporations, but also due to the impact they have in areas such as education or healthcare.

Every day more immersive healthcare applications are implemented, and new players are shaping the future of these technologies. As a key indicator, FDA has recently approved the marketing of the first VR treatment in their history, which uses cognitive behavioral therapy and other behavioral methods to help with pain reduction in patients with diagnosed chronic lower back pain.

Immersive therapy represents a new strategy in psychological interventions with promising results in general, but still far from being widely implemented. In this session we will review the application of a specific form of immersive technology, the immersive projection technology created by Broomx, a tech company from Barcelona. This tool transforms a room into a multi-sensory interactive experience that can be shared among several people without the use of VR headsets. It covers the user's field of vision with Full HD resolution and reactive audio, and it allows the user interaction with content projected in different ways. This technology has been used as a therapeutic tool in different healthcare projects, from a relaxation and stress reduction resource for health professionals during COVID-19 in a regional hospital in Spain to a non-pharmacological intervention in people with advanced dementia and Alzheimer in different senior care organizations in Canada and Europe, as well as a neurorehabilitation tool for patients suffering hemianopsia caused by a brain stroke or patients with persistent COVID symptoms. This session will give insights and references of different projects that have been developed using the immersive reality tool by Broomx, with real examples and key indicators.

Neurotechnology … What's next?

Carolina Aguilar
INBRAIN Neuroelectronics

The brain is the most intricate organ of all and the one that makes us human. Yet after centuries of healthcare development is the one that we know the least. Current technology and tools have been able to help us understand about 100,000 neurons or the brain of a zebra fish. However, human brain has nearly 100B neurons and not understanding it means we cannot find treatment for the 1 out 3 people in Europe that have a neuro-related disorder and which 30% are refractory to pharmacological treatment. But every leap in humanity have been linked to a key material, from stone age to silicon age today, we believe that novel materials such graphene can help us to undercover the mysteries of this incredible organ and leapfrog us to decode neural signals into new breakthrough medical solutions.

Will a digital copy of your brain help personalize therapies in patients suffering from brain disease? The future is here: Neurotwin

Ana Maiques
Neuroelectrics, Spain

The brain is a complex organ. One out of five people worldwide has developed a brain disease, like Depression, Alzheimer's, or Epilepsy. Unfortunately, for many of these diseases, there is no good cure, because medications do not work. For Neuroelectrics, the brain is not only a chemical body but also an electrical system. And from the electric perspective of the brain, they aim to diagnose and treat diseases using brain stimulation or electrical stimulation.

In this talk, Ana Maiques, CEO of Neuroelectrics, will dive deeper into the human brain presenting the Neurotwin project, a digital twin of the brain (aka digital copy of the brain) that allows personalized therapies in ways that had not been possible before. She will also share a concrete case on how Neuroelectrics is impacting the brain and the outcomes for patients.

The transition from research to day-to-day practice and how companies can help with the process

Andreu Oliver
Tobii, UK

These past five years have seen a boom in neurotechnology. The research that has been carried out for the past 30 is transpiring onto a trickling stream of start-ups that put into practice what was once impossible to imagine. Automatic diagnostic tools, early detection with digital biomarkers and much more. One only needs to look at the number of clinical studies being carried out to have a window into what will become possible in the coming years. At Tobii, we started enabling research 21 years ago. As such, we have been part of this process since the start, first accompanying the pioneers in their adoption of eye tracking to get a deeper insight into human behaviour. After that, we aspired to make the technology more affordable and user-friendly to allow more researchers to take advantage of it and use it to do their research. Finally, today, we are planning and structuring the company so that we can also accompany researchers on the path towards developing products that will impact the general population. With this, we also aim to accompany the researcher in the final step, where the research carried out during all those years comes to fruition and is transformed into a meaningful and impactful tool that will help people.

A single session of an attentional bias modification task based on virtual reality and eye-tracking to reduce attentional bias and body dissatisfaction in anorexia nervosa patients

Ascione, Mariarca (1); Carulla-Roig, Marta (3); Miquel, Helena (1); Porras-Garcia, Bruno (2); Meschberger-Annweiler, Franck-Alexandre (1); Serrano-Troncoso, Eduardo (3); Ferrer-Garcia, Marta (1); Gutierrez-Maldonado, José (1). Affiliation: (1) Department of Clinical Psychology and Psychobiology, UBneuro, Universitat de Barcelona, Barcelona, Spain; (2) Department of Population Health Science, University of Utah School of Medicine, Salt Lake City, Utah, United States of America; (3) Child and Adolescent Psychiatry and Psychology Department, Hospital Sant Joan de Déu of Barcelona, Esplugues de Llobregat, Spain.

Introduction: Anorexia nervosa (AN) patients show body-related attentional bias (AB), i.e., the tendency to focus more on self-reported unattractive and weight-related body parts than no weight-related body parts. Dysfunctional body-related AB has been associated with higher levels of body dissatisfaction (BD), one of the most important risk factors for the development and maintenance of eating disorders (ED) and could interfere with and reduce the efficacy of body exposure treatment used in patients with AN. The purpose of this pilot study is to assess the usefulness of a single session of an innovative body-related AB modification task (ABMT) that combines virtual reality (VR) with eye-tracking (ET) in AN patients. The goal of this ABMT is to reduce body-related AB. We expect that the AMBT will also be effective in reducing BD levels.

Method: Participants included 23 adolescent patients with a primary diagnosis of AN. Using a VR head-mounted display (HTC ® VIVE Pro Eye) with an ET device (Tobii ®), all participants were embodied in a virtual avatar with their real body measurements and body mass index, and were immersed in a virtual environment, characterized by a room with a mirror on the wall reflecting the avatar image. Both visuo-motor and visuo-tactile stimulation were used to create a full-body illusion (FBI), i.e., feeling the virtual body as their own body. Once the FBI was induced, the participant completed a single session of the ABMT, consisting of staring at geometrical figures appearing on specific body areas of the avatar's reflection, balancing attention between weight-related body areas and non-weight-related body areas. Body-related AB measures (as the complete fixation time - CFT - and the number of fixations - NF - on weight-related and non-weight-related body parts) and body dissatisfaction levels were assessed before and after the training.

Results: A paired samples t-test showed statistically significant differences between pre-assessment time and post-assessment time ($p<.05$) in reducing CFT on weight-related body parts and decreasing BD levels. There was no statistically significant reduction of NF on weight-related body parts.

Conclusion: This study provided initial evidence of the efficacy of a single session of a VR and ET-based ABMT in patients with AN in reducing and balancing body-related AB and decreasing BD levels. The current findings have important clinical implications since AB and BD are considered risk and maintenance factors for developing or maintaining ED symptomatology among patients with AN. For this reason, it is necessary adding specific components that aim to reduce body-related AB within AN treatment, such as body exposure therapy.

Attentional bias modification, through Virtual Reality-based body exposure, to enhance efficacy of treatment of anorexia nervosa

Meschberger-Annweiler, Franck-Alexandre (1); Ascione, Mariarca (1); Miquel, Helena (1); Porras-Garcia, Bruno (2); Exposito, Erik (1); Serrano-Troncosa, Eduardo (3); Carulla-Roig, Marta (3); Ferrer-Garcia, Marta (1); Gutierrez-Maldonado, Jose (1). Affiliation: (1) Department of Clinical Psychology and Psychobiology, UBneuro, University of Barcelona, Barcelona, Spain; (2) Department of Population Health Science, University of Utah School of Medicine, Salt Lake City, Utah, United States of America; (3) Child and Adolescent Psychiatry and Psychology Department, Hospital Sant Joan de Déu of Barcelona, Esplugues de Llobregat, Spain.

Introduction: Anorexia nervosa (AN) is an eating disorder (ED) characterized by low weight, body image disturbances (BIDs) and extreme fear of gaining weight (FGW) (APA, 2013). Mirror exposure therapies are considered effective interventions to help reduce AN symptomatology, especially the BIDs, consisting of an affective (body dissatisfaction) and perceptual (body distortion) component. However, efficacy of such therapies may decrease, due to attentional biases (AB) towards weight related body parts. The latest developments in virtual reality (VR) technology could overcome these limitations and allow AN patients to confront their FGW and BIDs. Our research group has been the first, to use VR technology with eye-tracking (ET) technology to investigate the attentional biases towards the body, providing new objective indicators (offered by ET instruments) in highly controlled situations and with high ecological validity (in VR immersive environments). Our current project aims to develop a VR-based attentional bias modification task (ABMT) reducing the body-related AB, and check if this component of reduction of bodily attentional biases increases the efficacy of a treatment of exposure to one's own body image that has already been studied in previous projects.

Method: The project includes several pilot studies with non—clinical female participants and one clinical study with AN female patients. Measures include main AN-related variables such as: Body Mass Index (BMI), BIDs through the EDI-3 inventory (Garner, 2004), body anxiety through the PAS-TAS scale (Reed et al, 1991), FGW through Visual Analog Scale. AB is assessed during a 30 seconds free exposure task to participant's avatar reflected in a mirror in VR environment, the fixation pattern being recorded through ET-tracking technology and processed by OGAMA software (Freie Universität, Berlin, Germany). ABMT consists in asking participant to gaze at geometrical figures projected on her avatar in a balanced way between weight and non-weight-related body parts, following procedure adapted from Smeets et al (2011). Participants are immersed in the VR environment designed with Unity 3D, using HTC VIVE Pro Eye head mounted display.

Results: Results so far have provided evidences about the existence of weight-related AB in women (Porras-Garcia et al, 2019), about the usefulness of VR-based body exposure to elicit FGW and BIDs in AN patients (Porras-Garcia et al, 2020), and about the mediation role of AB in the relationship between BMI and body dissatisfaction (but not distortion) (Porras-Garcia et al, 2020). In addition, another study revealed a significant reduction of FGW and BIDs after our VR-based ABMT intervention (Porras-Garcia et al, 2021). Finally, more recent study indicates that a significant reduction of weight-related AB starts after only 150 trials in VR-based ABMT (article under revision).

Conclusion: Results so far shows promising results about the validity of a VR-based ABMT to reduce body-related AB, and also to expand our knowledge about the underlying mechanisms contributing to the maintenance of AN symptomatology. We expect our ongoing clinical study, integrating such VR and ET techniques into body exposure therapies, will demonstrate a significant increase of their efficacy.

A Convolutional Neural Network approach for auditory stimuli classification from the frequency following response

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The frequency-following response (FFR) is a non-invasive scalp-recorded auditory evoked potential that reflects compound phase-locked neural activity elicited to the spectrotemporal components of the acoustic signal, along the entire auditory hierarchy (from cochlear nucleus, to midbrain, thalamus and cortex). A large body of evidence has demonstrated that the neuronal mechanisms involved in speech sound encoding, as reflected in the FFR, are related to speech-in-noise discrimination, reading skills and literacy, and can be tuned by language experience and musical training due to both short and long term experience-dependent plasticity. Disruptions in the FFR have been described in children with reading and language disabilities, and in neurodevelopmental disorders characterized by impaired communication and literacy skills, such as dyslexia or autism spectrum disorder.

In particular, infants born at term but small for gestational age are at high risk of neurodevelopmental delay. This condition, known as fetal growth restriction (FGR), affects by definition to 10% of the newborns but unless medical complication, babies are discharged without specific follow-up program. Yet, studies have identified that 40% of these infants will suffer neurodevelopmental delays, particularly in language acquisition, impacting their future reading skills and education. Previous findings from our lab revealed a lower SNR in FGR neonates compared to the average-for-gestational age (AGA) group in the absence of spectral amplitude differences.

Moved by these findings, we aimed at establishing the FFR as a biomarker of alterations in the neural encoding of speech. Our interest is focused on implementing a tool capable of classifying FFR depending on SNR parameters, and reducing the minimum possible number of trials due to the practical difficulties in recording brain activity in neonates. As a first approach to our goal, we have developed and trained a convolutional neural network (CNN) capable of identifying and classifying averages of 25 neural responses to two different types of auditory stimuli (|da| and |oa|) with accuracies up to 98%. The next stage will be to retrain the existing CNN to extend its capabilities to classify FFR not just by its auditory stimuli but by its related SNR parameters.

Neurotechnology: An upcoming revolution in science, medicine and society

Rafael Yuste

Neurotechnology Center, Columbia University, USA

The rapid development of neurotechnology, defined as methods to record or alter brain activity, will revolutionize science, medicine and the tech industry. In neuroscience, optical and nanoelectronic neurotechnological tools are enabling the systematic measurement and manipulation of brain activity in laboratory animals, providing deep insights into basic mechanisms of brain function. Similar tools, when applied to human patients, could enable a better understanding of the pathophysiology of mental and neurological diseases, likely leading to new therapeutics. Non-invasive brain-computer interface technologies will enable the direct linking of our brain to external computational devices, algorithms or memory storage. These advances could provide a new avenue of innovation and business opportunity for the tech industry, and lead to the mental and cognitive augmentation of our species. The application of neurotech is therefore poised to have a transformative effect upon humanity, with profound ethical and societal consequences intersecting with basic human rights such as mental privacy, free will and personal identity.

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Posters

1 UNC5-GPC3 interaction controls cortical migration by repulsion

Authors: Peregrina, Claudia (1); Zaballa, Sofía (1); Carrasquero, Maria (2); Kokolaki, Maria (2); Berbeira, Miguel (2); Seiraidake, Elena(2); Del Toro, Daniel (1). (1: Departament of Biological Sciences, Institut of Neurosciences, Medical School, UB, Spain). (2: Department of Biochemistry, University of Oxford, Ox1 3qu, UK)

Abstract: "During development, pyramidal neurons are born in the proliferative zone and radially migrate to settle in one of six cortical layers. We and others have shown that Uncoordinated-5 receptor D (Unc5D) regulates radial migration of cortical neurons independent of Netrin-1, suggesting the presence of other ligands. Our collaborators found that Unc5 receptors interact with the morphogen receptor glypican-3 (GPC3). Glypicans are expressed during central nervous system development but little is known about their function. By taking advantage of structured-based engineered mutants and anti-GPC3 nanobodies developed by our collaborators, we elucidate their role during cortical migration. Here we show that Unc5D is enriched in migrating cells while GPC3 is expressed in in radial glial cells during cortical development. Unc5D present in migrating neurons binds GPC3 in trans on opposing radial glial fibers. In stripe assays we show that GPC3 induces repulsion that is partially mediated by Unc5 receptors. Disrupting Unc5D-GPC3 interaction in vivo produces a strong delay in neuronal migration. Similar effects were seen after GPC3 knockdown in the developing cortex. Together out results show that Unc5D-GPC3 interaction controls the migration of cortical neurons in vivo."

2 Calcium/cation-mechanosensing ion channels activity are crucial mediators for mechanical induction of radial glia

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Abstract: "During brain development, radial glia is the principal embryonic neural stem cell and forms a radial palisade spanning the entire neuroepithelia. We have described that poly (methyl methacrylate) with 2µm linear topographies (ln2PMMA) mimic the structure of radial glia-niche. Ln2PMMA physical signals induce the conversion of cultured astrocytes into functional radial glia cells. However, the molecular mechanisms by which radial glia linage cells sense and respond to ln2PMMA mechanical signals remain poorly understood. We used primary cortical astrocyte cultures from newborn mice, grown for 3DIV in control (glass) and ln2PMMA substrates. We used a custom-developed high-throughput-like image analysis algorithm, allowing simultaneous correlation of lineage markers with nuclei morphology, at the single-cell level. We analyzed expression changes in mechanosensing ion channels by WB and RT-PCR. We validate Ca2+/mechanosensing cation channels implication by pharmacological inhibition of CaMKII (KN93) and non-selective cation channels (GsMTx-4). We finally perform Ca2+ imaging and microscopy cross-correlation to identify the activity of radial glia cells (Nestin+/Pax6+). Our first results show that Ln2PMMA significantly increase the number of Nestin+/Pax6+ radial glia cells. Cells in ln2PMMA significantly decreased TRPA1 and increased TRPC1 proteins. Moreover, ASIC1 mRNA significantly increased, with a protein increase at the limit of significance in Ln2PMMA. Pharmacological inhibition of CaMKII or non-selective cation channels prevents the increase of Nestin+/Pax6+ radial glia in ln2PMMA, although with a different effect on nuclear morphology. Finally, calcium/cation-mechanosensing ion channels activity are crucial mediators for the mechanical induction of astrocyte dedifferentiation into radial glia. Neural progenitors exhibit higher calcium activity and Ln2PMMA reduce intracellular calcium concentration and calcium transients."

3 Artificial Extracellular Matrix Scaffolds of Mobile Molecules Enhance Maturation of Human Stem Cell-Derived Neurons

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Abstract: Induced pluripotent stem cell (iPSC)-based technologies offer a unique resource for modeling development and disease of the human central nervous system (CNS). However, human iPSC models are still fraught with significant technical limitations including inefficient maturation and reduced long-term viability of neurons. These problems are in part due to a poor recreation of the native extracellular matrix (ECM) in vitro. We hypothesized that establishing a bioactive ECM environment that mimics the adult CNS would facilitate the functional maturation of iPSC-derived neurons. We utilized peptide amphiphiles (PAs) which self-assemble into supramolecular nanofibers that morphologically and chemically mimick the adult CNS ECM. We designed 4 distinct PA-nanofibers containing the bioactive peptide IKVAV found in Laminin-alpha-1, which is higher expressed in the adult CNS and plays a major role in neuronal behavior. The 4 IKVAV-PAs have an almost identical chemical composition, except for a 4 amino acids modification in the non-bioactive domain that makes the IKVAV epitope be displayed in a more or less mobile fashion. Interestingly, proteomic, biochemical and functional assays reveal that scaffolds with highly mobile molecules lead to enhanced beta-1-integrin pathway activation, reduced aggregation, increased arborization, and mature electrophysiological activity of human iPSC-derived neurons. Our work highlights the importance of designing bioactive ECMs to study the development, function and dysfunction of human neurons in vitro.

4 Role of RTP801 in adult hippocampal neurogenesis

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Abstract: Neurogenesis is the process of new neuron formation in the nervous system. This process is maintained throughout life in specific neurogenic niches. Among them, the dentate gyrus (DG) of the hippocampus is gaining attention given the role that adult hippocampal neurogenesis (AHN) has in cognition and memory. RTP801/REDD1 is a stress-induced protein that acts to inhibit mTOR signaling pathway. In addition, RTP801 has been linked to cortical development and neuroprogenitors' migration. In the present work, we studied the role of neuronal silencing of RTP801 in AHN in physiological conditions and in a murine model of AD, the 5xFAD. We observed that RTP801 knockdown in neurons tends to decrease the number of Sox2+ cells in the subgranular zone (SGZ) of the DG. In addition, the number of mature NeuN+ neurons increases when RTP801 is decreased. Altogether our results suggest that neuronal silencing of RTP801 increases the differentiation of

neural stem cells (NSCs) of the SGZ to mature neurons of the granular cell layer, thereby increasing the number of neurons in both control and AD conditions. This new putative role of RTP801 paves the way for further studies aimed to unravel the significance of such process but already suggests an important role in migration and differentiation of NSCs in AHN.

5 Long-term neuroepithelial-like stem cells as a model for dynamic monitorization of human neuronal network activity by calcium imaging

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Abstract: "Stroke is one of the most common leading causes of long-term disability worldwide. The pathophysiological mechanisms underlying stroke encompasses a series of complex events including metabolic stress, inflammation, neurotoxicity and, ultimately, cell death. Currently, the available therapeutic approaches are limited regarding timing and efficiency. In the last years, stem cell-based transplantation has emerged as a promising option for promoting functional recovery after ischemic stroke. Several in vivo and ex vivo studies with animal models have demonstrated the ability of committed neural stem cells to differentiate into a variety of neurons, integrate to host brain cells and establish functional synapsis with the host neural circuitry. However, evidence presume that the functional recovery observed in animals not only could be attributed to cell replacement itself but also to the so-called by-stander effect by which the release of several factors from these cells could have a positive impact on neurogenesis, neuronal plasticity, angiogenesis and immunomodulation. Recent technologies including GECI (genetically encoded calcium indicators), viral tracing methods, and optogenetics alongside the development of novel microscopy modalities has enabled the study of the electrophysiology, connectivity and functional integration of grafted cells in the host brain with an increasingly sensitivity and in a high-resolution manner. The main objective of the current project relies on the generation and transplantation of cortically committed long-term expandable neuroepithelial stem (lt-NES) cells into stroke-induced mice to subsequently study their connections with host brain areas, the functionality using a high-resolution scale microscopy methods and the spatial transcriptomic differences at a single-cell level. Here, we present the first steps beginning with the standardization of neuronal differentiation protocols including human induced pluripotent stem cell (hiPSC) derivation into lt-NES cells and their cortical-specific differentiation into mature neurons. Moreover, we used a GECI named GCaMP6s to perform long-term neuronal activity monitorization. Our results suggest that GCaMP6s expressing lt-NES cells are a suitable cell source for the following in vivo transplantation experiments into stroked mice brains."

6 Deep learning applied to live imaging for classifying brain organoids derived from dravet syndrome

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Abstract: Brain organoids are self-assembled in vitro 3D cell structures that recapitulate human brain development. In the last decade, brain organoids have risen as a powerful tool to study neurological disorders, including brain tumors and neurodevelopmental pathologies. However, brain organoids are intrinsically highly morphologically variable structures, thus limiting its use for obtaining reliable predictions of their phenotype and harnessing their scalability. Moreover, their analysis depends on highly trained human expertise and sophisticated technologies at end-point. Deep learning (DL) has reached human level performance for many so far machine-learning unsolvable problems. Here, we describe a DL approach to classify organoids upon a genetically driven neurodevelopmental disorder, such as Dravet Syndrome (DS). DS is a genetic epileptic encephalopathy with an early infancy onset driven by mutations in the sodium channel subunit gene SCN1A. Our multistep DL approach, herein named Image Phenotyping Network (ImPhenet), consists in the normalization of the microscopy live images followed by a predictive DL model to classify the organoids into healthy and DS. The ImPhenet framework shows a high performance in the classification of control and DS organoids, and can eventually be used as a model to determine the effect of drug on DS organoids. Altogether, we provide a proof-of-concept of the use of DL to determine the phenotype of neurodevelopmental disorder brain organoids and their implementation as a drug testing method.

7 Olfactory deficits in post-acute COVID-19: a Diffusion Tensor Imaging study

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Abstract: "Background: Neurologic symptoms have been reported in patients with coronavirus disease 2019 (COVID-19). According to a recent meta-analysis the prevalence of smell loss is 35-36% when measuring olfaction with validated tools (1). Despite the increasing interest in this matter, limited literature has focused on olfactory dysfunction's neural correlates throughout neuroimaging data. Objective: The aim of this research is to investigate whether white matter (WM) abnormalities are present in post-acute COVID-19 patients with persistent olfactory dysfunction compared to those with normal olfaction.
Participants and Methods: Forty-seven COVID-19 patients were (interval between the infection and the assessment in months, x = 10.1; SD=3.9) evaluated using diffusion-weighted on a 3T scanner. Whole-brain voxelwise statistical analysis of the fractional anisotropy (FA) and mean diffusivity (MD) data was carried out using Tract-Based Spatial Statistics (2) (TBSS) and FSL's randomize (3). The Smell Identification Test (UPSIT) (4) was used to measure olfactory function at the time of neuroimaging. Intergroup comparisons for DTI measures were computed, as well as correlations between DTI measures and the UPSIT. Results: Twenty-five patients were classified as normal or mild hyposmia and twenty-two as severe hyposmia or anosmia according to the UPSIT cut-off scores. Groups did not differ in age, years of education and sex. Patients with olfactory dysfunctions showed higher MD values in the genu of the corpus callosum, orbitofrontal WM tracts, the anterior thalamic radiation and the forceps minor compared to those with normal olfactory function (p=0.05). FA values were positively correlated with smell performance in the anterior thalamic radiation, the fornix, the forceps minor, and the corpus callosum (p=0.02), whereas MD values were negatively associated with this measure in orbitofrontal WM tracts (p=0.04). Conclusions: Our data suggest there is persistent decreased WM integrity that could explain prolonged olfactory deficits in post-acute COVID-19 patients.
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8 Pathophysiology characterization and treatment assessment of SARS-CoV-2 infection using brain organoids

Authors: Marti-Sarrias, Andrea; Turpin, Isabel

Abstract: The COVID-19 pandemic has resulted in more than 500 million cases in less than 3 years. SARS-CoV-2 virus has been reported neuroinvasive, neurotropic and potentially neurovirulent. Nevertheless, its pathophysiology remains obscure due to the impossibility to get parenchyma brain biopsies in living individuals. It is still not known to which extent the neurological manifestations are caused by direct viral brain invasion, by its replication, by systemic reactions to widespread inflammation, or their combination. Due to these ethical restrictions, drug testing of potential treatments is also a problem. Here, we use 3- and 6-month-old brain organoids developed from human embryonic stem cells to explore acute SARS-CoV-2 infection, assess the cell types that become effectively infected, and test the efficacy of potential antivirals that are already available for human use. Regarding the pathophysiology of the virus our results suggest that cells from choroid plexus from 3-month-old organoids can be infected, but the infection is more frequent in 6-month-old organoids. We also found that the virus cannot infect immature neurons, but they do infect MAP2+ ones and a large number of GFAP+ cells. Infection in old organoids also triggers astrocyte activation that could indicate an exacerbated neuroinflammatory response. Concerning drug evaluation, Remdesivir and Molnupiravir treatments showed to decrease the amount of viral load producing no toxicity.

9 Patterns of covariation between pre-pandemic resting-state functional connectivity and longitudinal loneliness experience during two years of COVID-19 pandemic.

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Abstract: "Background: The reduction in social interactions often associated with old age frequently initiates or aggravates loneliness, increasing the risk of several diseases including depression and dementia (Mushtaq et al., JCDR. 2014;8(9):E01–WE4.). Loneliness has been related to particular patterns of brain resting-state networks (RSNs; Spreng et al., Nat Commun. 2020;11(1):6393). However, the role of RSNs in a resilient response to reductions of social interactions remains

unknown and the COVID-19 pandemic provides an unprecedented opportunity to investigate it. Method: Twelve repeated loneliness assessments were collected by the Barcelona Brain Health Initiative (BBHI; www.bbhi.cat/en/) using the short UCLA Loneliness Scale (Russell et al., J Pers Assess. 1978; 42(3):290–294). Two timepoints were measured over two years prior to COVID-19 outbreak and ten thereafter. Particularly, loneliness scores were grouped according to pre-defined pandemic periods ranging from 2018 to Match 2022: pre-pandemic and six waves. We used baseline resting-state functional magnetic resonance imaging (rs-fMRI), from 281 participants (mean age 54.33±7.30; 127 women), acquired within 1-2 years prior to the pandemic to compute resting-state functional connectivity (rs-FC) for each pair of nodes defined by the Schaefer-Yeo atlas. Then, we utilized partial least squares (PLS) analysis for the decomposition of two multivariate sets (i.e., rs-FC and loneliness scores) into latent variables of maximal covariation. Results: We identified one latent trajectory significantly correlated with one latent connectivity pattern. This trajectory showed greater than average scores prior to pandemic that decreased until wave-2 and stabilized around population average from wave-4 to 6. The pre-pandemic rs-FC pattern associated with this trajectory was characterized by lower values of rs-FC within nodes of the Dorsal Attention Network and between these and the rest of the networks but the Salience Ventral Attention Network (DAN). On the contrary, the Fronto-parietal Control Network (FPCN) showed higher values of within rs-FC and between the Limbic, Somato-motor and Visual Networks. Particularly, the Default Mode Network showed lower rs-FC values between these last two networks, whose signals were at the same time more temporally correlated (i.e., greater rs-FC). Finally, the Limbic Network showed also greater rs-FC values between itself and the Somato-motor Network. Conclusion: Present findings reveal specific associations between baseline RSNs' functional connectivity and non-average longitudinal changes in feelings of loneliness during an unanticipated period of severe social restrictions. Specifically, a generally less connected DAN and stronger connections between the FPCN within and Limbic Network nodes, were predictors of this specific trajectory. Interestingly, the present study also presents particular results involving associations between sensorial networks. These could hint specific less known roles of these areas in psychological processes that should be explored in future studies."

10 Sex-based differences in the acute effects induced by N-ethyl-pentylone. Locomotion and immediate early genes expression.

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Abstract: "The synthetic cathinone N-ethyl-pentylone (NEP), also known as 'ephylone', is one of the novel psychostimulants that has recently emerged into the illicit drug market. NEP is currently one of the most reported new psychoactive substances (NPS) and several intoxication cases and even fatalities have been associated with its consumption. Nevertheless, little is known about potential sex-dependent differences in the effects of NPS. Accordingly, the main objective of the present study was to investigate possible sex-based differences concerning hyperlocomotion and immediate early genes (IEGs) expression induced by different doses of NEP. Male and female Swiss CD1 mice (eight-week-old) were exposed to an acute intraperitoneal (i.p.) injection of saline (0.9% NaCl) or 1, 3, or 10 mg/kg of NEP, and their horizontal locomotor activity was recorded during the two following hours on an open field arena. Once the locomotion was evaluated, mice were immediately euthanized by cervical dislocation, and the dorsal striatum (DS), ventral striatum (VS), and medial prefrontal cortex (mPFC) areas were dissected out. The expression of the IEGs arc and c-fos was assessed in DS and VS and bdnf mRNA levels were evaluated in mPFC. Acute administration of 3 and 10 mg/kg NEP induced higher hyperlocomotion in males than in females when normalizing against their corresponding saline group. In addition, the hyperlocomotion lasted up to 100 min. in males after the 3 mg/kg injection while females just showed increased locomotion during 35 min. Moreover, while the hyperlocomotion induced by 10 mg/kg NEP lasted 85 minutes in females,

the locomotor activity remained increased for two hours in male mice. Concerning the IEGs expression assay, male mice showed a higher increase in arc and bdnf mRNA levels compared to females after a 10 mg/kg NEP injection. On the other hand, despite no sex differences were observed in c-fos mRNA levels, both sexes overexpressed this IEG in DS and VS. Therefore, our results suggest that increased c-fos mRNA levels after acute NEP exposure can induce a response of neuroplasticity in males and females. However, the different overexpression on arc and bdnf suggests that this drug could induce more pronounced and lasting modifications on synapses in males than it would trigger in females. If translated to humans, these differences might account for different abuse potential of this substance between males and females."

11 Sexual differences in brain connectomics and protein expression after cognitive stimulation in the TgF344-AD rat model

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Abstract: "Background: Cognitive reserve explains interindividual variability in coping with cognitive decline associated to ageing or Alzheimer's disease (AD)[1]. Research into the networks involved in cognitive resilience may help to determine the mechanisms of cognitive reserve. The TgF344-AD rat model (TG) of AD shows time-dependent alterations revealing dysfunction in specific resting state (RS) networks[2]) and structural network reorganization with an impact on cognitive abilities[3,4].
We have investigated the impact of early cognitive stimulation on functional and structural connectivity in a longitudinal experimental design, using wildtype (WT) and TgF344-AD (TG) male and female rats.
Methods:Cognitive stimulation consisted of initial training (≈2 months) and periodically performing of the Delayed Non-matched to Sample (DNMS) task [3] from 3 to 18 months. The experimental groups were: Untrained animals: WT n=11; TG n=11; Trained animals: WT n=8; TG n=12. RS-fMRI and DWI sequences were acquired in a Bruker BioSpec 7T scanner. Details of the MRI acquisition sequences can be found in [3,4]. Structural and functional brain networks were estimated and characterized by graph metrics. RS networks were calculated by independent component analysis using FSL MELODIC[5] with the whole cohort. Graph metrics, amplitude and shape were computed for each subject and the differences between groups were evaluated using MLE models. After 18 months of age, animals were sacrificed, and brains were processed for immunostaining and western blot analysis.
Results: MLE model analysis showed significant ($p<0.05$) interaction of cognitive stimulation and genotype factors only in males for two structural connectome measurements: strength and clustering coefficient. This result suggests and effect of early cognitive stimulation in TG animals not observed in the WT. RS-fMRI analysis are currently being performed. Interestingly, western blot analysis showed a trend to increased -catenin expression in the cortex of TG males, while in TG females a significant ($p<0.05$) increase of ARC protein was observed. In both TG male and TG female rats GAP43 was significantly ($p<0.05$) increased in the stimulated group. -catenin has been related in anti-A aggregation processes, ARC in memory and LTP and GAP43 in vesicular neurotransmitter release.
Conclusions: Male TgF344-AD rats have increased structural connectivity measures after cognitive stimulation compared to the non-stimulated group. Early training increases the expression of proteins involved in synaptic plasticity in a sexual dependent manner. Further analysis are need to better interpret our results that certainly point to a positive impact of early cognitive training in brain connectivity.

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12 MonteCarlo simulation in nuclear imaging: toward accurate quantification methods

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Abstract: "Nuclear imaging, including Single Proton Emission Tomography (SPECT) and Positron Emission Tomography (PET), facilitates the diagnosis of neurodegenerative diseases such as Parkinson's or Alzheimer's Diseases (PD, AD) as it allows the in vivo evaluation of brain´s neurotransmitters, metabolism and aberrant protein accumulation. Although diagnosis is typically based on qualitative assessment performed by experienced observers, image quantification can improve diagnostic accuracy and allows studying scalable relationships with other non-imaging variables. To this end, it is necessary to provide standardized and precise quantification tools. We use MonteCarlo simulations to obtain synthetic PET and SPECT images using realistic maps of activity that describe the alterations typically found in different pathologies, and which can be used to evaluate the accuracy of quantification methods across radiotracers and pathologies.
In this work, we provide a comprehensive methodological explanation together with application examples of the utility of simulations. The main elements needed for obtaining simulations are: (1) activity input maps, created by mimicking pathological effects on individual anatomical segmentations, typically derived from Magnetic Resonance Images (MRI); (2) attenuation maps, derived from individual skull segmentation; and (3) characterization of the acquisition system, including its geometry and the system response to the simulated energy photons. Using this procedure, it is possible to create a simulated database of subjects with different uptake alteration degrees. As these sets are simulated from user-defined activity maps, real values -i.e., ground truth maps- are known, making this approach very suitable for testing and comparing any quantification method and processing tools and makes also possible to study the effect of different reconstruction parameters in the quantification. Several examples of application include quantification in dopaminergic neurotransmission SPECT, 18F-FDG-PET in epilepsy or PD, and Amyloid-PET or Tau-PET for simulating different AD stages."

13 Epidemiology of dementia in the very young and the oldest old - insights from prescription claims in Austria

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Abstract: "Background: The epidemiology of dementia is shifting. Diagnostic improvements increase the identification of early onset forms while longevity increases dementia in the elderly. Unfortunately, only little data is available on these cohorts. We used a prescription claims database to analyse the changing relationship of age and incidence at the tails of the distribution, thus including very young and very old people with dementia. Methods: The database included >98% of all insured persons in Austria covered by federal social security institutions and recorded prescription claims from 2003 - 2016. Patients who were prescribed one ADD, i.e. either donepezil, galantamine, rivastigmine or memantine, were in-

cluded. These drugs can only be prescribed after the diagnosis of dementia is made by a specialised physician. We identified patients aged <65 years (very young) or >=85 years (oldest old). Census and survival data was obtained through a public registry. Prevalence was calculated at the time of database closure as a percentage of the overall insured population and CI were calculated using the Clopper-Pearson method. Incidence was defined as de-novo treatment with an ADD between 2014 and 2016. Kaplan-Meier curves for survival were constructed and compared using the logrank test. Calculations were performed using R 4.0.2. Results: The database included 74506 patients currently/previously on ADD. Of those, 3613 (4.8%, 95% CI: 4.7 - 5%) were between the age of 35 and 65 years, and 18913 (25.4%, 95% CI: 25.1% - 25.7%) were over the age of 85. The median age in the very young group was 59.7 (IQR: 54.9 - 62.9) and 51.3% of these patients were female; the median age in the oldest old group was 87.9 (IQR: 86.3 - 90) and 76.7% were female. During a median follow up of 3.47 (IQR: 1.84 - 4.81) years for the very young and 1.91 (IQR: 0.87 - 3.45) years for the oldest old, 14.3% in the early onset and 56.2% in the oldest old died, respectively. Assessing each cohort individually, we find that in both cohorts mortality increased significantly with each age group (p log-rank <0.001). Prescription incidence was recorded from 2014-16 and 31695 patients started ADD treatment. Of those, 1107 (3.5%) were <65 and 10560 (33.3%) were >85. Cumulative incidence was 0.07 / 1000 person years in the very young and 12.5 / 1000 in the oldest old. Incidence rates increased linearly in the very young age groups while they decreased in the oldest old. There was no difference in incidence rates when grouping by sex. Discussion: A prescription of ADD in young people is rare but increases linearly with age, suggesting an interplay of age and heritable risk. Antidementive medication is frequently started in the oldest old and Gender did not appear to confer substantial risk in both cohorst. These results can contribute to improved diagnostic and therapeutic approaches for this population."

14 SREG: A pipeline for unbiased, robust and smooth nonlinear longitudinal registration of 3D brain scans.

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Abstract: "Background: Longitudinal image analysis has a wide range of applications in brain studies; for example, in evaluating disease modifying therapies or designing subject-specific diagnostic protocols. Some of the main challenges are related to the introduced processing bias, to the differences in acquisition protocols (within- and between-subject) or to the variable number of follow-up visits at irregular intervals. In this work we introduce a processing pipeline that tries to address the aforementioned points. The goal of the present article is to show the utility of the pipeline in three different applications that can serve as a proof-of-concept for deformation-based analysis using "SREG". Pipeline: We present "SREG", a pipeline for longitudinal image processing of T1-w MRI and compatible with BIDS format (Fig. 1). For each subject, it first pre-process the images, then determines a latent -unseen- subject space via rigid alignment of all timepoints and then computes a more accurate subject-specific template using non-linear diffeomorphisms. The template is saved in subject space as well as in MNI space. Finally, it also outputs a refined segmentation using the label-fusion approach in [1] The core of rigid and non-rigid alignment is performed in the log-space, i.e., the relationship between the fields is linear. Initially, we compute a pairwise registration between all timepoints; afterwards, we optimise a graph structure to find a deformation (rigid, non-rigid) to a latent, unknown template such that minimises the error from the pairwise registrations. Since the optimisation is carried on the log-space, the optimisation is linear and could be found using linear programming (l1-norm) or closed form solutions (l2-norm). The computed deformations can then be used for downstream tasks, such as segmentation or prediction. The novelties of SREG with respect previous approaches are two-fold: on the one hand, as compared to the Freesurfer processing pipeline [2], it is faster and computes non-ri-

gid deformations; on the other hand, as compared to the diffeomorphisms computed by [3] it is unbiased, robust to registration errors and provide smoother trajectories by design. Experiments: We use the publicly available MIRIAD dataset [4] consisting of N=69 subjects (N_NonDemented=23, N_Demented=46) that have been scanned at irregular intervals from 2 weeks to 2 years. We perform three experiments to evaluate the utility of the pipeline and compare with previous methods. First, we want to assess the volumetric trajectories at the ROI level between the Freesurfer segmentations, both from the cross-sectional (FS-CROSS) and longitudinal (FS-LONG) pipelines and the refined segmentation from our pipeline (SREG). For that, we fit a linear-mixed effects (LME) model on several subcortical ROIs with random intercept and slope. When comparing the effects on the trajectories, our performance improve the original segmentations and is comparable our competitor in [2]. Second, we want to assess the trajectories at the voxel level. In this case, we compute the mean trajectory per subject and project it to the MNI space for comparison across subjects. There, we compute the Jacobian determinant and perform a simple t-test between diagnostic groups for all voxels. Our results are consistent with the literature and different regions around the ventricles survive the most conservative Bonferroni correction over the p-values. Moreover, we find larger statistical significance as compared to LAITS_DD, the work presented in [3]. Finally, we fit a linear model to the deformations to inter- and extrapolate a subject-specific evolution. Conclusions and future work: We have shown the utility of SREG and trajectory-based models. We plan to apply this pipeline in other datasets and use the computed trajectories in multiple applications, such as in subject-specific prognosis with complex models or causal inference."

15 Episodic memory dispersion influences cognitive performance and structural brain connectivity in a healthy middle-aged sample

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Abstract: "Background: Cognitive dispersion (CD), a measure of intraindividual variability across neuropsychological tests, has been proposed as an independent predictor of cognitive decline and prodromal stages of dementia (Thaler et al. J Clin Exp Neuropsychol. 2015;37(6)622-629). In addition, CD has been associated with alterations in brain integrity (Halliday et al. Front. Hum. Neurosci. 2019;13(352)). Our aim was to investigate, in a healthy middle-aged sample, the associations between CD and cognitive performance (CP) considering 3 main cognitive domains: episodic memory (EM), speed of processing (SOP), and executive function (EF). Furthermore, we wanted to study their neurobiological substrates using structural and functional magnetic resonance imaging (MRI). Method: Five hundred forty-four healthy volunteers (aged 53.11±7.10 years; 269 female) from the Barcelona Brain Health Initiative cohort (BBHI, https://bbhi.cat/en) were analyzed. CD and CP were based on the EM, SOP, and EF scores. CD values were calculated by the intraindividual standard deviation method (Costa et al. Clinic Neuropsychol 2019;33(2):369-389) and CP factors were estimated using a principal component analysis (PCA) for each cognitive domain (i.e., for CD: EM-D, SOP-D, and EF-D; and for CP: EM-P, SOP-P, and EF-P). Diffusion tensor imaging (DTI) and resting-state functional MRI (rs-fMRI) scans were acquired. For DTI images, fractional anisotropy (FA) values were obtained by tract-based spatial statistics (TBSS) from FSL as a measure of white matter integrity. In addition, resting-state functional connectivity (rs-FC) within networks were computed through the Shirer atlas (Shirer et al. Cerebral Cortex 2012;22(1):158–165). Statistical analyses included univariate ANCOVA

GLMs and partial correlations adjusted by age, gender, and framewise displacement (for rs-fMRI data). Results: Despite there was no association between CD and CP for each specific domain, we identified a negative correlation between EM-D and SOP-P (r=-0.104, p=0.017), and EF-P (r=-0.090, p=0.037). The MRI findings only revealed negative correlations between EM-D and FA comprising the longitudinal, fronto-occipital, and anterior thalamic radiation fasciculus. Nevertheless, no associations were found between CD and CP measures and rs-FC values. Conclusion: Our findings highlighted that EM-D has a clearly measurable impact on a healthy middle-aged sample, both in terms of its effect on CP and structural connectivity. These results suggested the value of considering CD measurements as a more sensitive marker than CP to white matter fiber integrity alterations (i.e., lower FA), an early typical age-related change."

16 Associations between Repetitive Negative Thinking and brain segregation amongst healthy middle-aged and young-old adults.

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Abstract: Repetitive Negative Thinking (RNT) is a psychological construct associated with persistent negative thoughts about the future (worry) and past (rumination), and it has been previously linked to anxiety and depression. RNT also relates to low self-perceived cognitive functioning as well as increased cognitive decline and neuroimaging Alzheimer's disease (AD) biomarkers. Evidence suggests that prefrontal and anterior cingulate cortices are vulnerable key regions to RNT but several other brain areas within large-scale networks are also involved, the efficiency of which depends on their ability to remain segregated. System segregation (SyS) decreases with age and it has proved to be associated with clinical decline regardless of AD pathology. Associations between RNT and SyS of the Anterior Salience Network (ASN), Default Mode Network (DMN) and Executive Control Network (ECN) were explored in healthy middle-aged and young-old adults (N=341) drawn from the Barcelona Brain Health Initiative (BBHI) cohort. All participants underwent magnetic resonance imaging with a 3Tesla Magnetom Prisma (Siemens Medical Systems) at the Hospital Clínic, Barcelona. A 10-minute resting-state functional magnetic resonance imaging and a high-resolution 3D image were acquired. Preprocessing of resting-state images was carried out with FMRIB Software Library, FreeSurfer 6.0 and Statistical Parametric Mapping (SPM12). The Shirer atlas was used to compute brain segregation and functional connectivity values for each targeted network; namely ECN, DMN and ASN. Regression analyses were conducted with RNT as the outcome variable. Explanatory variables were: SyS, depression, emotional stability, cognitive complaints, age and sex. Results indicated that RNT was associated with depression, emotional stability, cognitive complaints, age and segregation of the left ECN (LECN) and ASN. Specifically, higher levels of perseverative thinking were related to increased segregation of the LECN and decreased segregation of the ASN. Post-hoc analyses indicated that the ventral DMN (vDMN) presented higher coupling with the ASN and decreased connectivity with the LECN, as a function of RNT. Our analyses indicated associations between RNT and segregation of frontoparietal-executive and limbic-related networks, which are linked to cognitive control, attention and emotional regulation. The dissociative connectivity of these networks with the vDMN may partially account for poorer cognitive control and increased self-referential processes characteristic of RNT. System segregation, understood as the balance of between-network and within-network connectivity might be a biomarker of RNT among healthy middle-aged and young-old adults.

17 A home-based cognitive intervention improves social cognition in children with cerebral palsy

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Abstract: "Objective: Children with cerebral palsy (CP) have social cognition difficulties that impact their everyday life. Rehabilitation interventions in children with CP mainly target motor impairment, which is the central diagnostic feature of CP. Some interventions are focused on cognitive associated impairments, but it is unknown if these interventions exert short- and long-term improvements in social cognition. The aim of the present study is to explore whether a computerized executive function training programme can improve social cognition functioning in children with CP. The potential retention of intervention effects 9 months after completing the assessment is also explored. Participants and methods: Sixty children with CP were paired by age, sex, motor, and intelligence quotient (IQ) and then randomized to intervention or usual care. Thirty participants (8 to 12 yo, mean age 10.29, SD 1.65; 15 females) underwent a home-based computerized executive training programme that also includes social cognition tasks (12 weeks, 5 days a week, 30 minutes per day training, total dose 30 hours). The remaining thirty children (mean age 10.01, SD 1.73; 15 females) were assigned to the usual care wait-list group. Motor severity of the 60 children was mild and IQ ranged from 75 to 125. Social cognition was assessed by the Theory of Mind and Affect Recognition subtests from the Developmental NEuroPSYchological Assessment-II (NEPSY-II). Assessments were performed at three time points: before, immediately after and 9 months after completing the training. Social cognition differences between groups were assessed by analysis of covariance, including pre-training performance as a covariate. Strengths and Difficulties Questionnaire (SDQ), Autism Spectrum Screening Questionnaire (ASSQ), Parental Stress Scale (PSS), Beach Center Family Quality of Live Scale (fQOL), and pain frequency were also included as covariates. Results: The intervention group showed a significantly better performance immediately after training in Affect Recognition (F=6.9, p=.011, n_p^2 =.126) but not in Theory of Mind (F=.6, p=.435, n_p^2=.085). Improvements in Affect Recognition were maintained 9 months after training (F=4.5, p=.039, n_p^2 =.074). In addition, although Theory of Mind improvements were not reported just after intervention finished, delayed effects were found 9 months later (F=11.8, p=.001, n_p^2 =.179). Conclusions: Undergoing an executive function training programme exerts a positive effect on social cognition. Results also support the retention and, interestingly, the long term-effects of this intervention. Our findings highlight that including social cognition tasks on cognitive interventions in children with CP could be a cost-effective intervention with short- and long-term effects."

18 Children with cerebral palsy improve their visual perception skills after undertaking a computerized cognitive intervention

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Abstract: "Introduction: Visual perceptual functioning is considered a core deficit in children with cerebral palsy (CP) that may have an impact on daily life. Evidence about the far transfer effects of computerized intervention in visuoperception has recently increased. In the present study we aimed to test the effect that an executive function on-line and home-based intervention program has on visuoperception and visuospatial skills in children with CP. Patients and methods: Sixty children with CP from 8 to 12 years old (mean age 10.15 years, SD 1.69, 30 females) were paired and randomized to executive function intervention (30 min, 5 times per week, 12 weeks) or usual care group. Visuoperception and visuospatial skills were assessed through Benton Facial Recognition and Arrows (NEPSY-II) tests, respectively. Analyses of covariance with baseline scores as covariate were performed to compare the intervention and control group at post-treatment. Results: Children that underwent the intervention presented with significantly better visual perception skills than the control group (p=0.047, partial eta-squared [n_pˆ2] = 0.68). No significant improvements were found in visuospatial skills (p=0.267, n_pˆ2 = 0.022). Conclusion: Twelve weeks of home-based executive function intervention improves visuoperception skills in children with CP. These findings align and add further information to previous studies about the transfer effects on visuoperception after physical and cognitive computerized interventions not targeted to visual perceptual functioning. Future research is needed to better understand which specific features of the interventions have an effect on improving visual perceptual skills in children with CP."

19 Math anxiety and response inhibition in a Go/NoGo task

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Abstract: Previous studies have reported a deficit in executive functions in highly math-anxious (HMA) individuals, specifically in the interference control. However, no study to date has investigated whether math anxiety is also related to a deficit in behavioral inhibition. Behavioral inhibition is an important component of attentional control that allows us to suppress an overbearing response or inadequate action in a given context. The aim of this experiment was to examine whether HMA individuals have a deficit in behavioral inhibition when performing a task with numerical stimuli. Sixteen HMA and 17 low math-anxious (LMA) participants were asked to perform two Go/No-Go tasks. In the numerical task, single-digit numbers were presented on the screen and they were asked to press a button if the number was even and made no response for odd numbers. In the non-numerical task, letters were presented and participants were asked to press a button if the letter was a vowel and withhold it if a consonant appeared. Go and NoGo trials were randomly presented with a 4:1 probability for the "Go" answer to be more frequent. Groups did not differ in RT for the Go trials, although responses to numbers were slower than responses to letters. As for hit rate, more errors were committed in NoGo than in Go trials for both groups in both tasks. Importantly, the Go-NoGo difference in hit rate was larger in the numerical than in the non-numerical task only for the HMA group; i.e., it was harder for this group to withhold pressing the button in No-Go trials in the numerical than in the non-numerical task. This result suggest that HMA individuals might have a deficit in the response inhibition at behavioral level when they deal with numbers, what could contribute to their low achievement in math tasks.

20 Virtual Self: The psychological relevance of online videogames in identity construal

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Abstract: "With the Internet becoming such a widespread part of our lives, many notions of how we construe our identity have changed, and another layer of complexity has been added to an already deep subject. The anonymity of the Internet and the capacity to customize how other people see us makes it possible for anyone to create their own virtual identity with a considerable and unusual level of freedom. This is especially relevant in massive multiplayer online role-playing games (MMORPGs), where players interact with each other in open virtual environments through customizable three-dimensional avatars. This project aims to study how people construe their identities within those virtual environments. More specifically, it is meant to study how MMORPG players use their avatars to explore different alternative identities. Some people could modify their avatar and their in-game behavior to perform different versions of themselves, such as an idealized version compensating for some lacking in real life, or even explore an entirely separate identity to experience what would it be like to be someone else. There are also several variables that might influence how this virtual identity manifests. Some of these variables are inherent to the player as a person, such as their cognitive complexity, self-esteem or psychological well-being. Others may be more related to the specific game they play, such as the level of immersion experienced or the main motivational factors for playing. To explore this phenomenon, the authors are using the constructivist Repertory Grid Technique, which allows the study of a person's construal of themselves, their ideal self and several other people in their lives, including their main character in an online videogame of their choice, which will be labeled as their "virtual self". By exploring the proximal relationship between the actual, virtual, and ideal self, the authors proposed a theoretical typology of the different ways in which online videogame players can construe their virtual identity according to its psychological meaning. There are three main categories:
• The projection type, where the players perceive themselves as different from their ideal self and create a virtual self that resembles more their ideal self and is more distant from their actual self.
• The exploration type, where the players see themselves as more similar to their ideal self and then create a virtual identity that is completely different from both their actual and ideal selves.
• The proximal type, where the players create a virtual self that is more similar to their actual self, regardless of how they perceive themselves.
There is a fourth theoretical category, the unspecified type, where the actual, ideal and virtual self are equally distant from each other. While mathematically possible, no previous literature has been found that supports its existence.
This typology will be validated using the Repertory Grid Technique and cluster analysis. Other instruments will be administrated to study the personal and game variables that could affect how people construe their virtual identity or be associated with certain categories within the proposed typology. This project aims to study how people construe their identities within those virtual environments. More specifically, it is meant to study how MMORPG players use their avatars to explore different alternative identities. Some people could modify their avatar and their in-game behavior in order to manifest different versions of themselves, such as an idealized version of themselves in order to compensate for some lacking in their life, or even explore an entirely separate identity to experience what would it be like to be someone else. There are also several variables that could modify how this virtual identity manifests. Some of these variables are inherent to the player as a person, such as their cognitive complexity, self-esteem or psychological well-being. Others may be more related to the specific game they play, such as the level of immersion experienced or the main motivational factors for playing. To explore this phenomenon, the authors are employing the Repertory Grid Technique, which allows the study of a person's perception of themselves, their ideal self and several other people in their lives, including their main character in an online videogame of their choice, which will be labeled as their "virtual self". According to how similar or different the actual, virtual, and ideal self are from each other, the authors designed a theoretical typology of the different ways in which online videogame players can construe their virtual identity. There are three main categories:

• The projection type, where the players perceive themselves as different from their ideal self and create a virtual self that resembles more their ideal self and is more distant from their actual self.
• The exploration type, where the players see themselves as more similar to their ideal self and then create a virtual identity that is completely different from both their actual and ideal selves.
• The proximal type, where the players create a virtual self that is more similar to their actual self, regardless of how they perceive themselves.
There is a fourth theoretical category, the unspecified type, where the actual, ideal and virtual self are equally distant from each other. While mathematically possible, no previous literature has been found that supports its existence.
This typology will be validated using the Repertory Grid Technique and cluster analysis. Other instruments will be administrated to study the personal and game variables that could affect how people construe their virtual identity or be associated with certain categories within the proposed typology."

21 Self-dialogue with Virtual Future Self about Nicotine Dependence

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Abstract: "When we have a personal problem, we tend to keep talking to ourselves by engaging in an internal monologue to find a solution, often going around in circles never reaching a conclusion. However, when a friend or colleague presents a problem to us, we are usually above to give good advice. In other words, we can often give better advice to a friend than we can to ourselves. This observation gives rise to the idea of using virtual reality as a tool to create a self-counselling experience, where a person can have a dialogue with themselves, as if they were the friend with a problem. Virtual Reality (VR) self-counselling includes interaction between two virtual bodies: a virtual body that is a virtual replica of the self, and a virtual body of another person, representing, for example, a counsellor. Participants explain a personal problem to the counsellor when embodied in their own body, and then from the embodied perspective of the counsellor see and hear themselves explain the problem, and then give advice to themselves from this perspective. In this way, participants can see and hear themselves from the perspective of another. Essentially they become like the 'friend'. Previous research has indicated that, this type of self-dialogue in virtual reality can result in improved mood and increased sense of having been helped leading to a change when participants discussed a personal problem that causes mid-level stress in their daily lives. Studies of the neural correlates of self and others demonstrated that perspective taking is associated with the activation of the medial prefrontal cortex (mPFC) both for the first person's perspective and third person's perspective even though the activation is greater when perspective taking takes place in the first person. In addition, a positive association between self-reassurance and the activation of the ventromedial prefrontal cortex (vmPFC) has been found. When participants take the perspective of the counsellor, we might expect the activation of the mPFC and the vmPFC due to the activation of the concept of self and self-reassurance. To investigate the potential clinical applications of this mechanism, we have focussed on the problem of addiction by applying this self-counselling method to understand its possible advantages for people with tobacco use disorder who want to give up smoking. Instead of a counsellor, the discussion is with an older version of the self who has given up smoking years before and managed to maintain that. The idea is that the future self will explain how she or he was able to do that. This is based on the idea of future self-continuity - the possible impact of sharing similarities between the present self and future self as well as perceiving future self vividly and po-

sitively. The hypothesis is also that people do generally know how they might stop an addiction, but from the perspective of the future self it is easier to access and articulate that information. We randomly assigned participants into three different conditions: Future Self Non-Smoking, Future Self Smoking, Current Self. In this way, we aim to investigate the difference between negative and positive versions of the future self while using the lookalike body as a control condition during the possible modulation of nicotine dependence on Stages of Change of smoking, physical dependence, levels of smoking and behavioural dependence. We expect to find a reduction in the Stages of Change of smoking, the physical and behavioural nicotine dependence levels for people who experienced future self conditions compared to those who experienced current self condition. The research is ongoing and we will present the up to date results of the study at the conference. The project that gave rise to these results received the support of a fellowship from "la Caixa" Foundation (ID 100010434) with the fellowship code LCF/BQ/DR19/11740007 and the European Research Council Advanced Grant MoTIVE: Moments in Time in Immersive Virtual Environments (#742989)."

22 Sound sequence recall on a self-generation paradigm: an electrophysiological study

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Abstract: Self-generation effects describe attenuated sensory processing for self-generated (SG) stimuli compared to externally generated (EG) ones. In parallel, the production effect suggests that SG stimuli are differentially encoded in memory. However, literature on the relationship between these these two effects is still scarce. The main aim of this study was to assess whether self-generation effects on sensory processing underlie or relate to subsequent production effects on memory for SG sounds. As information encoded in memory is organized into discrete episodes we hypothesized that actions may not only modulate the strength of memories for SG stimuli, but they may additionally structure the encoding of events in memory, creating differentiated memory representations for SG and EG stimuli. We designed a delayed match-to-sample task in which consecutive SG and EG sounds were delivered, creating two different context-episodes within a 9-sound sequence (encoding phase). After a short retention period, we presented a pair of test-sounds which could be formed either by across-context (SG-EG, EG-SG) or within-context (EG-EG, SG-SG) sounds (retrieval). Participants responded whether the pair of test-sounds was presented in the same order as during encoding. Using EEG, we measured self-generation effects on sensory responses to the sounds during encoding. Result showed that the N1 and P2 components of the auditory ERPs were attenuated for SG compared to EG sounds. However, despite this differentiated sensory processing during encoding, behavioral analyses failed to reveal memory performance differences between across-context and within-context pairs. Moreover, if there was a production effect, there should have been a memory advantage for SG sounds compared to EG sounds. However, performance for SG-SG pairs was not significantly different from EG-EG pairs. The present findings suggest that the suppression of sensory responses for SG stimuli does not influence memory encoding of these stimuli, pointing to a lack of direct relationship between the known self-generation effects (on sensory processing) and the production effect (on memory).

23 Neural signatures of memory gain through active exploration in an oculomotor-auditory learning task

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Abstract: Active learning – being able to control information while learning – has been shown to enhance memory in different domains. Further, stimuli generated by oneself as opposed to an external source trigger attenuated neural responses and are remembered better ("production effect"). Studies using event-related potentials have shown that the neural attenuation of responses to self-generated visual or auditory stimuli is frequently linked to the Sense of Agency (SoA) – the subjective experience of causing our own actions and their sensory consequences. However, the coincidental presence of movement during sound processing has also been shown to attenuate neural responses, regardless of whether there was causality between action and sound, and whether the sound was intentionally generated. The current study asks whether agency over an auditory stimulus alone, controlling for the movement factor, can enhance memory formation and affect ERPs. Participants learned associations between the movements of a cursor and 8 different sounds. Critically, the cursor was controlled either by their own eye movements (active learning) or by an external agent (passive learning). During fixed time intervals, participants memorised movement-sound associations by actively exploring them or passively watching a guided exploration. Later, their memory was tested presenting movement-sound pairs that either matched or mismatched the learnt associations. Since there were eye movements in both conditions, we were able to study the effect of agency while controlling for the effect of movement. By comparing ERPs during early (when participants are unfamiliar with the movement-sound associations and sound identity is therefore unpredictable) and late stages of learning (where sound identity is predictable), we were further able to analyse the effect of predictability on ERPs, independently of agency and movement. We found that participants were able to learn movement-sound associations faster in the active learning condition. On a neural level, ERPs time-locked to the onset of sound stimuli showed that learning progress was linked to an attenuation of the P3a component at fronto-central sites. Active control over sound stimuli was reflected in ERPs in a large positive deflection starting around 200ms post-stimulus at parietal sites. During memory tests, the detection of matching movement-sound pairs triggered a late parietal positivity, which could be understood as a target-matching P3b response. Although we did not find modulation of the N1 component across all subjects, we found a correlation of the difference between active and passive N1 amplitudes with performance on the memory task. We found that subjects with a stronger self-generation effects (attenuation of the N1 component for actively generated sounds) had a stronger memory gain for actively acquired associations. Our results show that the SoA alone, independent of movement, helps learning and memory and modulates sensory responses. Further, we found that individual differences in the N1 attenuation effect for self-generated sounds predict the strength of the production effect. Taken together, these results help to disentangle the effects of agency, unspecific motor-based neuromodulation, and stimulus predictability on ERP components and establish a link between self-generation effects during processing and the production effect.

24 Neurophysiological mechanisms of auditory processing during movement: Evidence from electroencephalography and pupillometry

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Abstract: Biological organisms are constantly bombarded with a flux of sensory information that needs to be adequately processed for optimal interaction with the environment. Yet, what we perceive is not just a mere reproduction of the signals reaching our sensory organs. Instead, we interpret the external world through an interaction between the self and our environment. A specific instance of this interaction is how we process and memorize the sensory outcomes of our own actions. Although substantial work has been done in this domain, mainly showing attenuated perception and sensory processing for self-generated information, several issues remain unknown, often leading to heated debates as for the mechanisms underlying the differential processing of self-generated stimuli. At the core of this debate stand questions related to the direction of the action effects on behaviour (i.e., suppression or enhancement of memory) and sensory processing (i.e., cancellation or sharpening of sensory responses), the nature of the effects (i.e., stimulus-specific motor-predictions or unspecific mechanisms possibly driven by neuromodulatory processes), but also the influence of other factors that are often confounded with self-generation (e.g., predictability). The present work attempts to elucidate the mechanisms underlying the effects of actions on auditory processing. In two original studies, we examined the self-generation effects from the angles of memory encoding and basic physiology, namely electrophysiological responses and neuromodulatory processes (i.e., measured with pupillometry). Specifically, we addressed the effects of actions on sensory processing and memory encoding by employing self- and externally-generated sounds that differed or not in their predictability. Meanwhile, our work was the first to assess the involvement of neuromodulatory processes in the action-induced modulations of auditory responses and whether they are shaped by predictability. On the behavioural level, we showed that actions modulate memory performance, but the direction of the effects depends on predictability confounds and the type of movement that triggers the sound. Specifically, when predictability is not controlled and actions are cued, memory performance drops and relates to the magnitude of the attenuation effects for self-generated sounds. In contrast, in the absence of predictability confounds (i.e., when self- and externally-generated sounds are equally predictable or unpredictable), the mere presence of a self-paced action enhances memory performance of sounds, but this enhancement does not relate to the suppression effects. Related to the effects of actions on sensory processing, we showed that the suppression effects are not only driven by stimulus-specific predictive processes and that they do not only reflect modulations in sensory-specific areas. Additionally, pupil diameter increased during actions, interacted with predictability, and was linked to sensory attenuation when the effects were strongest (i.e., fully predictable contexts). Taken together, the present work disentangled the contribution of factors other than self-generation in modulating memory and neurophysiological responses for self-generated inputs (i.e., predictability), proposes a neurophysiological mechanism that could explain the link between the motor-induced suppression and subcortical neuromodulation, and shows that actions trigger a cascade of stimulus-specific and unspecific processes – presumably driven by subcortical neuromodulatory processes – that collaboratively orchestrate auditory processing and memory encoding.

25 How humans adapt visual sampling to the temporal structure of a dynamic environment.

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Abstract: "In our daily lives, relevant events may occur at different times and in different spatial positions. Suppose someone is driving along a motorway; they would need to adapt the time during which they monitor other lanes to the speed of the cars in those particular lanes (i.e. monitor more often where speed is higher). Therefore, optimal temporal monitoring would need to collect information about the temporal structure of the events around us (e.g. for how long a relevant event will be detectable in some particular place). We designed a behavioural task to investigate whether humans are able to use optimal strategies to monitor different locations based only on the temporal structure of the environment. The task was an analogy of a situation where the passengers of a car in the central lane must monitor both the lanes on their left and right to detect any moving cars that might overtake them at different speeds depending on the lane. The lane at which the advancing car could appear and its onset were randomly determined, and they could be detectable for 0.5 seconds in the fast lane or for 1.5 seconds in the slow line. Participants could choose which lane to monitor at any time, while the other lane would always be darkened and out of sight. We manipulated both the general speed of the cars, which determined the duration for which they could be detectable (multiplying their duration by 1, 1.5 or 2) and the time needed to alternate the area of vision from one lane to the other (either 0.5, 0.75 or 1 second). By looking at how frequently participants switched between lanes and how long the fixations at each lane lasted, we can extract an observation pattern that reflects how they distribute their monitoring time between lanes and compare this pattern to an optimal observer. A model that describes an optimal observer is proposed and used to compare how well participants adapt to these changes in the temporal structure of the environment. Even though participants generally used a fairly good strategy and adapted their sampling differentially to the different lanes' temporal structure, they failed to conform to optimal patterns and achieve full optimality."

26 Establishment of a murine preclinical model of retinitis pigmentosa type 10 to decipher the pathophysiological mechanisms of retinal neurodegeneration

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Abstract: INTRODUCTION: Inherited retinal diseases affect 1 in 4000 people severely compromising their vision. They are caused by mutations in more than 200 different genes, being clinically heterogeneous. Among them, retinitis pigmentosas (RPs) are caused by genetic mutations that affect rod function, manifesting primarily as night blindness and gradually progressing to the loss of central vision. There is no current treatment for most forms of RP. Retinitis pigmentosa type 10 (adRP10) is caused by gain of function mutations in the genes that codes for Inosine Monophosphate Dehydrogenase 1 (IMPDH1). IMPDH1 catalyzes the rate-limiting step in the novo synthesis of guanine nucleotides, impacting the cellular pools of GMP, GDP and GTP. How Impdh1 mutations are specifically deleterious to photoreceptor cells of the retina is not yet known. However, recent crystallographic studies on IMPDH proteins of eukaryotic origin (Buey et al. Nature Communications 2015); and a study on IMPDH1 role and regulation in dark/light conditions in the retina in vivo (Plana-Bonamaisó et al. eLife 2020) have led to a clear hypothesis. HYPOTHESIS: Impdh1 mutations would cause photoreceptor cell death by disrupting a GDP/GTP sensor in the protein´s regulatory domain, responsible for nucleotide allosteric inhibition of the enzyme. By disrupting this allosteric

control, linked to protein filament formation, mutations would lead to constitutive enzymatic activity and/or irreversible filament accumulation, ultimately deleterious for photoreceptor cells. RESULTS: We here report the generation of a mouse model of adRP10 (D226N/IMPDH1) by using the CRISPR/Cas9 technology. Preliminar analysis of D226N/IMPDH1 mice have shown that heterozygous mice for the mutation manifest retinal degeneration and loss of visual function over time. The number of photoreceptor cells is reduced by 35% in D226N/IMPDH1 mice versus littermate controls at five weeks of age. This neurodegeneration correlates with a reduction in the A- and B- waves of the electroretinogram (ERG) response to light flashes in the scotopic and mixed range. The D226N mutation also leads to the formation of protein aggregates, observed in retinal sections as cytoophidia or spicula at the photoreceptor cell layer. CONCLUSIONS: we have established a preclinical mouse model of adRP10, the D226N/IMPDH1 mice that mimics the phenotype of adRP10 patients. D226N, the most prevalent mutation in Spain and in the USA, presents a gain-of-function mode of inheritance. The D226N mutant protein forms cellular aggregates that accumulate over time. FUTURE STUDIES will address whether the levels of IMP, GMP, GDP, GTP and cGMP nucleotides are affected in D226N/+ versus +/+ littermate controls, affecting photoreceptor conductance; and whether the accumulation of aggregates leads to endoplasmic reticulum stress as the main cause of cell death. Ultimately we will look for therapeutic means to delay the rate of neurodegeneration in order to preserve visual function in this preclinical model of disease.

27 Fast auditory responses to threat sounds presented at high temporal modulations in a fear conditioning paradigm

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Abstract: Neural models for emotional processing in vision suggest the existence of an ultrafast route to the amygdala, a critical structure for threat processing, which allows for fast detection of threat and subsequent adaptive behavior in humans. This fast route is known to involve magnocellular neurons mediating coarse visual processing, and to elicit response to threat, in amygdala and visual cortices, at earlier latencies than other slower, more fine-grained, pathways. In the auditory domain, animal evidence suggests the existence of a similar ultrafast route for threat detection, but it still remains unknown in humans. In this study, we investigated whether a similar fast, magnocellular pathway to the amygdala might mediate fast responses to threat in the auditory system, based on evidence that magnocellular auditory neurons are particularly sensitive to high temporally modulated sounds. We used a fear conditioning task, which depends on amygdala response, while recording electroencephalogram (EEG) in 29 healthy participants. Subjects had to behaviorally detect human voices, which were either paired (conditioned stimuli, CS+) or unpaired (non-conditioned stimuli, CS-) with an unpleasant loud white noise (unconditioned stimulus, US). Thus, CS+ voices acquired threatening significance, whereas CS- voices, or the same CS+ voices before conditioning, remained emotionally neutral. All voices were amplitude modulated at either high (40 Hz) or low (10 Hz) rates, aiming to differentially activate a fast (magnocellular) versus a slower (parvocellular) auditory pathway, respectively. Preliminary results suggest that fear conditioning was effective, as participants were aware of the pairing (contingency) between the CS+ and the US, with increasing awareness towards the end of the experiment. Subjects also rated CS+ voices as being more emotionally negative and alerting during conditioning, relative to the same stimuli in a PRE-conditioning block (i.e., before conditioning took place). These results indicate that participants learned the CS+/US association in the task. Detection of voices (hit rate) was higher for voices presented at high amplitude modulations (High AM), relative to those at low AM in POST-conditioning block. However, this was only true for CS+ voices, and not for CS- ones. Finally, High AM conditioned (CS+) voices elicited increased auditory cortical responses, compared

to responses to the same stimuli before conditioning, at a very early latency (14-68 ms), whereas such increased response was only apparent at later stages (around 200 ms) for Low AM CS+ voices. Taken together, these results suggest that threatening stimuli presented at high AM rates elicit increased auditory cortical responses that are compatible with an ultrafast amygdala response, and subsequent fast modulatory inputs from the amygdala to the auditory cortex, as opposed to overall slower responses to threat at low AM rates. Thus, high amplitude modulated sounds may be an optimal tool to differentially activate and investigate a putative fast auditory route to the amygdala, similar to that in the visual system.

28 Background noise effects on neonatal frequency-following response (FFR)

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Abstract: "Background noise influence in speech perception has been studied across the age span and it has been linked to different language and developmental disorders. Nevertheless, to the best of our knowledge and despite its importance, speech-in-noise (SIN) has not been thoroughly investigated in newborns. Considering that the frequency-following response (FFR) has been used in SIN studies due to its sound mimicking characteristics, it could emerge as an effective tool to assess this phenomenon in newborns. The present study aims to compare how background noise could modify speech encoding in neonates and adults through the analysis of their FFRs. Participants were 16 healthy-term neonates (aged <48h afterbirth) without auditory risk factors, and 25 normal-hearing adults (aged 20-40 years). FFR were recorded to a 170 ms syllable /da/ of fundamental frequency (F0) of 113 Hz presented at 65 dB. Noise condition was assessed by playing a Spanish six-talker babble noise at -10 dB signal-to-noise ratio. Several FFR parameters were retrieved from the recordings in time and frequency domains. Results showed that whereas adults exhibited larger spectral amplitude to the speech stimulus in quiet condition than in noise condition, newborns spectral amplitude did not differ significantly in the quiet condition or with background noise. This study constitutes the first step towards understanding the development of SIN encoding from the very first moment of life. Speech-in-noise encoding in newborns did not seem to be affected by auditory challenging environments, perhaps due to their perhaps due to their auditory system only being exposed to attenuated sounds during gestation.

29 Disentangling the effects of prenatal music exposure on neonatal neural speech encoding

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Abstract: It is known that fetal hearing experiences shape linguistic and musical preferences of newborns from the very first moment of birth. Thus, neonates prefer their native language, recognize their mother's voice and show greater responsiveness to lullabies presented during pregnancy.

Yet the neural underpinnings of this experience inducing plasticity have remained elusive. Here the frequency-following response (FFR), an auditory evoked potential from cortical and subcortical origin, was used to show that prenatal music exposure enhances the neural encoding of the stimulus pitch along the auditory hierarchy at birth. FFRs were recorded in a sample of 60 healthy term newborns during their first hours of life, divided into two groups according to their musical exposure during the last trimester of pregnancy (29 high-musically exposed; 31 low-musically exposed), as reported by their mothers through a questionnaire. Neonatal FFRs were recorded to either a /da/ or an /oa/ stimulus, analyzed during a section in both stimuli identical in duration (113 ms) and pitch (fundamental frequency, F0 = 113 Hz), and quantified as the spectral amplitude to the stimulus F0. Analysis revealed that neonates exposed daily to music exhibited larger spectral amplitude at F0 as compared to the low-exposed group, observing this effect across stimuli. Results indicate that prenatal musical exposure enhance the encoding of low-frequency components of sounds, such as those typical of the human speech, suggesting that this exposure modulate the tuning to human speech and support the early language processing and acquisition mechanisms.

30 The role of the nature/type of tasks on the choice between tasks with different effort levels

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Abstract: "Research associated to cognitive demand demonstrated that everything else being equal, between two tasks with different levels of cognitive demand, there will be a bias against the task with higher demand, as it is stated in the law of least mental effort. Considering that cognitive effort is inherent to cognitive control, because I higher level of cognitive control in a task entails a higher effort sensation than more automatics tasks, past studies usually examined the bias of choice between tasks with different level of cognitive control. The demand selection task is the most used type of task in these experiments, where the participants have to choose freely between two tasks with different levels of cognitive control. For the purpose of evaluating the influence of the nature of the task on the choice, the task was manipulated in order to have a more motivated task than the ones that traditionally are used within this paradigm. Therefore, the aim was to study whether the preference of choice towards the least demanding task would depend on the nature of the task. Consequently, the subjects were divided in two experimental groups. The group with the most motivating task, a priori, performed a verbal analogy task, whereas the other group performed a numerical task-switching task. In addition, taking into account that there is a lot of factors that may influence the decision, we decided to measure the switch cost as a measure of the cost of cognitive control, the perceive fun and effort level, the need for cognition (which is a disposition where people like to engage in cognitive demanding tasks) and self-control scale. The main hypothesis was that the numerical switch task group would choose, as studies showed, the low demanding task but the analogy group would choose the high demanding task. We did a repeated measured ANOVA for the proportion of choice between the easy and the difficult deck with the type of task as a group factor. The results reveled that the easy task was the preferred option but there was not a significant group effect, showing a general choice tendency towards the least demanding task, according to the law of the least mental effort.
Regarding the other variables we did a correlation analysis, and we applied the Šidák correction. We did not find any correlation for the numerical task group. For the analogies group, even though we found a correlation for the fun index, perceiving the demanding task as funnier, it did not influence the decision. There was, as well, a relation between the Need for Cognition and the choice of the most demanding task in the analogy group. In conclusion, the study didn't prove that the nature of the task established the choice of the task depending on the complexity, in accordance to the least effort law. Nevertheless, taking into account the association of the need for cognition and the fun of the task, it is possible that there are intrinsic motivation factors that can influence the decision."

31 Assessing the relationship between neural entrainment and altered states of consciousness induced by electronic music

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Abstract: "Music plays a pivotal role in all ritualistic contexts. Its sonic characteristics change depending on its function. In electronic dance music festivals, the highly rhythmic and repetitive beat of electronic music seems to be used to produce altered states of consciousness (ASCs) and facilitate the life-shaping experiences that the attendees crave. This observation has evoked comparison to the absorptive continuous drumming used in shamanic rituals to go into spiritual journeys. From a neuroscientific standpoint, several neural mechanisms have been suggested to explain how exposure to repetitive sounds might induce ASCs. The one that has received the most attention is entrainment, the natural synchronization of brainwaves to the phase of periodic external stimuli. However, the relationship between entrainment and ASCs has not been systematically explored before. The current study aims to shed light on this relationship for the first time by using naturalistic electronic music. We drew upon the finding that the rate at which repetitive sounds are presented modulate the magnitude of entrainment, reaching a peak at around 2 Hz. This observation led us to examine whether changes in the magnitude of entrainment to songs presented at different tempos were related to measures of ASCs. In our experiment, 20 naïve participants listened to six one-minute long electronic music excerpts that could be categorized into three different tempos (i.e., 1.65 Hz, 2.25 Hz and 2.85 Hz; two songs per tempo). After listening to each musical excerpt, rhythm-induced ASCs were measured with cognitive tasks and a retrospective questionnaire about participants' phenomenological experience while listening to the music. Brain activity was recorded with electroencephalography during the whole duration of the songs to measure entrainment. Our results revealed that the tempo of electronic music modulated entrainment and some phenomenological aspects of ASCs. When measuring entrainment as an average response to the one-minute long stimulation period, entrainment was lower for music at 1.65 Hz compared to the ones played at 2.25 Hz and 2.85 Hz. However, when taking into account the temporal dimension of entrainment, our results revealed that, for most part of the one minute of stimulation, entrainment at 2.25 Hz was higher compared to the other slower and faster tempos. Regarding the behavioral measures of the rhythm-induced ASCs, participants experienced more feelings of unity when listening to the slowest music, at 1.65 Hz, compared to the faster ones, at 2.85 Hz. Critically, we found moderate relationships between participants' scores in the retrospective questionnaire and entrainment only for music at 1.65 Hz. Although we also found a weak relationship between participants' cognitive function and entrainment at other tempos, these results might be explained by modulations in the endogenous neural activity on the delta frequency band that might be relevant for the cognitive tasks. Taken together, our findings provide a potential physiological mechanism, entrainment, to explain the usage of repetitive sounds to produce ASCs. Also, our results highlight the importance of taking into consideration the complex temporal dynamics of entrainment when working with numerous stimulation rates."

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32 Neural development of the speech-sound encoding abilities in healthy infants during the first six months of life

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Abstract: Language acquisition is a unique expertise that infants are able to master at very early stages of development. Speech perception and its developmental milestones are depicted across the literature for the first months of age in different populations and languages. However, the neural mechanisms underlying these maturational processes are still poorly understood. Here, we use an auditory evoked potential termed frequency-following response (FFR) to unravel the developmental trajectory of the neural encoding of speech sounds during the first six months of age. The FFR is elicited to periodic sounds such as speech or music, and allows evaluating the tracking accuracy of complex sound features in the auditory hierarchy. Moreover, it can be modulated by musical and language exposure and it appears disrupted in children with speech or language impairments and neurodevelopmental disorders, which supports the aim of using this response as a possible biomarker for speech encoding impairment and literacy achievements. The FFR was elicited to a tailored novel stimulus /oa/, which allows analysing specifically the neural encoding of the stimulus envelope and of its temporal fine structure (Arenillas-Alcón et al., 2021 Sci. Rep.). Recordings were obtained in a sample of 54 healthy-term neonates at birth and retested at the age of six months. Six parameters were extracted in the time and frequency domains to characterize the FFR. Results revealed a shortened neural lag and a maturation of the stimulus temporal fine structure neural encoding as a function of age, while no significantly different stimulus envelope encoding was observed across the two time point measurements. This study adds new knowledge to the literature, describing the striking maturation of the fine structure encoding abilities, already present at the early age of six months. It further contributes to characterize the neural developmental trajectory behind speech perception abilities during the very early stages of life and supports its use to assess early abnormalities that could be associated to later language impairments.

33 Unraveling the anatomical basis of the neonatal frequency-following response: a combined MRI-EEG study

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Abstract: From the third trimester of pregnancy, the developing human brain follows a series of maturational patterns, including myelination of white matter (WM) fibers, cortical gyrification, and increased gray matter (GM) volume. These can be decoded and related to functionality with techniques such as magnetic resonance imaging (MRI), magneto-, and electro-encephalography (M/EEG). Volumetric anatomo-functional correlates of the frequency-following response (FFR) have never been assessed in the neonatal population. Yet, several studies in adults have related the volume of certain auditory brain regions such as the GM section of the primary auditory cortex (PAC)

and superior temporal gyrus (STG) to hearing abilities, IQ, and language function, therefore motivating the present study. Here, we aim to explore the anatomo-functional relationship between auditory and language regions' volume (insula, corpus callosum, STG, medial and inferior temporal gyrus) and the FFR metrics (pitch measures, fundamental frequency, and temporal fine structure) at birth using EEG and MRI. To do so, structural MRI and FFR data were collected from a sample of 31 healthy term neonates, pre-processed, and analyzed. Correlations of ROIs volume index with FFR parameters showed a greater contribution of WM regions than GM ROIs. Results also point out a significant role of STG's and medial and inferior temporal gyrus (MITG)'s volume on pitch measures. In contrast, corpus callosum (CC) volume stands out in the temporal fine structure.

34 Self-monitoring of information richness in second language vocabulary learning

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Abstract: "Self-monitoring of information richness in second language vocabulary learning Active learning is a critical component of human development, however, the mechanisms supporting it are not fully understood. One of the core components of active learning is information seeking (IS), or the capacity to spend resources in an intrinsic motivated long-term goal. A key aspect in IS is being sensitive to the informational richness of a given context, which might allow to regulate the cost (or resources) dedicated to implementing successful activities that will end up information gains (i.e., learning). The present work aims to provide new evidence regarding how learners select information and implement IS strategies. To achieve this objective, a sample of 17 healthy 9-11 year old children was selected. A word learning task that consisted of 80 pairs of Spanish sentences ending with an unknown pseudoword was created and calibrated for the target sample. Participants needed to guess the meaning of that pseudoword in order to achieve as much points as possible (points are interchangeable after the experiment for small presents). Participants, in each trial had the possibility to request more information that could help to discover the meaning of the new word. Requesting more information involved losing some points from the total they might win. Two aspects were critical in the task created: (i) the level of Difficulty of the word learning task (richness of the context) and the Cost of points that will cost when requesting more information (clues). Results showed the main effects of Cost and Difficulty: there was a higher demand of info-clues in the difficult compared to the easy condition as well as in the low-cost compared to the high cost condition. Additionally, there was an interaction between these two factors. No differences were found in the demand of clues by difficulty, when the cost of clue does not bring any possible benefit. The present results support the idea that children have the capacity to self-monitor information richness in learning conditions and correctly ask for help to keep learning in certain conditions depending on the cost of the investment."

35 Cognitive control and pre(SMA)white matter system in Huntington´s Disease

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Abstract: "Cognitive control understood as the process supporting flexible, adaptive responses and complex goal-directed thought, comes as a necessary step in language production anytime a

speaker needs to actively select a needed word from a set of competing options (=language cognitive control). A functional neuroanatomy candidate which may be a key territory for language and (language) cognitive control is represented by the pre-supplementary and supplementary motor areas ((pre)SMA). (Pre)SMA cortical territory is connected with the frontal cortex and caudate nuclei through an extensive system of white matter fibers. The major components of this system include the frontal aslant tract (FAT, projecting towards inferior and middle frontal gyri) and fronto-stratial tract (FST, projecting towards caudate nucleus). However, the involvement of these connections in language production in not fully understood. Huntington's Disease (HD) represents a pathology of genetic origin which is strictly related to degeneration at the level of the brain cortex and striatum. Importantly in this sense, previous studies pinpoint difficulties that individuals with HD experience in language and cognition, all of which makes HD a perfect candidate for studying structure-to-function associations of the (pre)SMA system. Additionally, to the uniqueness of HD at the anatomical level, this pathology can be genetically detected before the onset of symptoms during its pre-manifestation phase. This offers a chance to detect the threshold at which white matter degeneration is severe enough for language or cognitive impairments to develop. The aim of the present study is to explore the involvement of the (pre)SMA system in cognitive control by testing relationships between the microstructural properties of the (pre)SMA connectivity and scores on relevant cognitive tasks.
The microstructural data from our subjects was extracted using probabilistic tractography and diffusion-weighted images (DWI). To do so, we used already existing DWI data from 47 HD patients (25 manifest and 22 premanifest) and 35 healthy controls. Cortical regions of interest (ROIS) were defined in standard space according to the Harvard-Oxford neuroanatomical atlas (available in FSL). The caudate nucleus was defined using an automated method (FSL FIRST). To enhance anatomical precision, these ROIS were then transferred to each subject´s native space, revised, and used as seeds for probabilistic tractography (FSL Probtrackx). The tractography results will be then used to extract microstructural measures (fractional anisotropy, mean diffusivity), and tract volume. As cognitive tasks whose scores will be compared with the microstructure of the tracts, we will use the Stroop task (response inhibition), Trail Making test B-A (mental flexibility), Backward Digit Span (working memory), and verbal fluency test (lexical selection). Results of these tasks are already available, and the last steps of the relevant analyses are ongoing. This analysis will allow exploring, for the first time, which portions of the (pre)SMA white matter system are the best at explaining variability in performance on various facets of cognitive control. They will also test if structure-to-function relationships are more pronounced in the manifest HD gene carrier versus premanifest."

36 Deregulated plasma extracellular small RNAs as a promising biosignature for premanifest Huntington's Disease

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Abstract:"Despite the advances in the understanding of Huntington's disease (HD), no disease-modifying treatments exist, and therapeutic development and HD-clinical trials continue to fail. Major efforts are focused on the assessment of measurable outcomes for optimal therapeutic response. Recent insights on HD described small non-coding RNA (sRNA) as key players in the disease. The profiling of extracellular sRNAs (exRNA), found in body fluids as freely circulating, associated to protein-complexes, and/or encapsulated in extracellular vesicles (EVs), supposes a promising approach for defining non-invasive biomarkers. Using an optimized method for plasma sub-fractionation and

EVs purification by Size-exclusion chromatography (SEC) and Ultrafiltration (UF), we explored sRNA content in EVs and Non-EVs compartments, providing a deep exRNA analysis and offering a complementary source of valuable information. Characterization of plasma-EVs from three different cohorts, including healthy controls, premanifest HD, and manifest HD, revealed no differences in size and morphology of EVs. Using SeqCluster bioinformatic tool for sRNA annotation and quantification, we highlighted that most differentially expressed (DE) sRNAs in HD-EVs are downregulated in comparison to Control-EVs, with many changes occurring at premanifest stages. In addition, those DE sRNAs in EVs showed a strong correlation with cognitive symptoms. Otherwise, in the Non-EVs compartment, miRNAs appeared upregulated in HD patients. Selected sRNAs showing the most differential profile between groups were validated by RT-qPCR in additional samples as potential future biomarkers for HD. In conclusion, these findings suggest that EVs and Non-EVs plasma compartments offer complementary and valuable information, reflecting early clinical and pathological changes in HD patients. The deregulation of exRNAs could constitute a biosignature for the progression of HD, improving the sensitivity of protein-based biomarkers at the premanifest stage.

37 Lack of corticostriatal VPS13A induces hyperlocomotion and neuronal plasticity defects in a chorea acanthocytosis mouse model

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Abstract: "Chorea-acanthocytosis (ChAc) is a rare autosomal recessive neurodegenerative disorder caused by a VPS13A gene mutation leading to marked reduction or absence of VPS13A. ChAc patients show adult-onset progressive movement disorders such as chorea, dystonia, parkinsonism, seizures, peripheral neuropathy, and red blood cell acanthocytosis. The main neuropathological feature in ChAc is a selective degeneration of the striatum. The study of the VPS13A function in the brain has been poorly addressed due to the lack of mouse models. Therefore, the objective of this work is (1) to develop a ChAc cell and mouse model using miR30-based shRNA knock-down (KD) system and (2) to evaluate how synaptic plasticity and neuronal function in corticostriatal circuits are affected when VPS13A is down-regulated. First, we evaluated the efficacy of three miR30-shRNA to knock-down the VPS13A expression. We found a significant reduction of the VPS13A mRNA and protein by qPCR and western blot, respectively, and a tendency to decrease VPS13A staining intensity by immunocytochemistry in STHdhQ7/Q7 cells. Then, we encapsulated the two most promising miR30-shRNA in an AAV viral vector to generate the cellular and the KD mouse model. To generate a cellular model, we infected primary cortical and striatal neurons with both AAV-shCtrl and AAV-KD. We observed a reduction of the 80% of VPS13A protein in AAV-KD cultures compared with AAV-shCtrl. AAV-KD primary cortical neurons also presented a decrease in the number of intermedia branches and a reduction of the total branch length compared with AAV-shCtrl neurons. However, we found no differences in any of the parameters analyzed in AAV-KD primary striatal neurons compared with AAV-shCtrl cells. To generate a mouse model, we performed a stereotaxic surgery in 8-week-old mice. AAV-shCtrl and AAV-KD were injected bilaterally in M2 cortex and in two different regions of the striatum. At 12-week-old, we observed a reduction of VPS13A protein in M2 cortex and in the striatum of KD mice by western blot (reductions of 40% and 50%, respectively). Behavioral tests revealed hyperlocomotion and an increment in the exploratory behavior in KD mice. However, these mice did not show alteration in motor learning or in motor coordination and balance. Furthermore, KD mice did not exhibit anxiety-like behavior or compulsive-like behavior. At the cellular level, although KD mice did not show motor impairment, we observed a significant reduction of the PSD95 protein levels (post-synaptic marker) in both M2 cortex and striatum, but we did no see differences regarding synaptophysin protein levels (pre-synaptic marker) when com-

pared with controls. In addition, KD mice presented a tendency to decrease TrkB receptor protein levels and a significant reduction of BDNF in both M2 cortex and striatum. These results suggest a role of VPS13A in the control of neuronal plasticity mechanisms. Understanding how the absence of VPS13A modulate synaptic function will contribute to further knowledge of ChAc pathophysiology. Supported by grant from the Ministerio de Ciencia y Innovación (PID2020-119386RB-I00) and Fundación ChAc (Spain)."

38 Novel optogenetic tools to modulate cAMP in neurons: Effects on Huntington's disease

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Abstract: In neurons, cAMP modulate metabotropic responses and induce many intracellular signalling pathways, including synaptic plasticity. Phytochrome photoreceptors can act as adenylate cyclase and produce cAMP in cells upon photoactivation, allowing spatio-temporal modulation of cAMP, which can be particularly relevant in neurodegenerative diseases such as Huntington's disease (HD). HD is characterized by motor disturbances, associated to a progressive disconnection of the cortico-striatal circuitry. Therefore, our main goal is to evaluate the potential of phytochromes as a novel tool to induce long-term neuronal plasticity in HD's specific brain circuits. We evaluated how cAMP modulates neuronal activity dynamics by analysing Fluo4 calcium fluorescence intensity changes, as well as individual and collective spontaneous neuronal activity by Forskolin application, in WT and R6/1 mice primary cortical cultures at 14 DIV, using the NETCAL software. We observed that Forskolin increases the number of neurons firing collectively, while single neuronal activity (number of spikes, ISI, IBI) remains unaltered. Moreover, this effect was not observed in HD cultures. We also ensured that Forskolin was increasing cAMP levels by fixing the cultures one hour after the exposition to Forskolin and analysing pCREB levels, both in WT and R6/1 cortical neurons. Accordingly, primary cultures from WT and HD were infected at 7 DIV with an AAV expressing Phytochromes (AAV9-CamKII-DdPAC-Flag-tag) and calcium dynamics induced by phytochrome activation are currently being analysed. We are also implementing fiber photometry tools to study phytochrome effects in vivo by using the calcium sensor GCamp6f. Altogether, these results contribute to the development of new approaches towards modulating brain activity and uncover circuit dynamics in Huntington's disease.

39 Neuroprotective effect of EGCG against Huntington's disease induced by 3-NP

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Abstract: "Huntington's Disease (HD) is a neurodegenerative disorder that affects 5-10/100.000 individuals in developed countries. Clinically, it is characterized by cognitive and behavioral alterations and a severe dysfunction in motor skills. However, little is known about the mechanisms implicated in such disease's progression, leading to a lack of an effective treatment. Epigallocatechin-3-gallate (EGCG) is a natural product which origin resides in Camellia sinensis, a green tea plant. This polyphenol has antioxidant and anti-inflammatory pro40 Is RTP801/REDD1 involved in tRNA processing?Authors: Campoy Campos, Genís (1,2,3); Torres, Adrián Gabriel (4,5); Solana-Balaguer, Julia (1,2,3); Pérez-Sisqués, Leticia (1,2,3); Alberch, Jordi (1,2,3,6); Pérez-Navarro, Esther (1,2,3,6); Ribas de Pouplana, Lluis (4,5,7); Malagelada, Cristina (1,2,3) Affiliation: (1) Universitat de Barcelona, Facultat de Medicina i Ciències de la Salut, Unitat de Bioquímica, Barcelona, Catalonia, Spain; (2) Institut de Neurociències, Barcelona, Catalonia, Spain; (3) Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain; (4) Institut de Recerca Biomèdica (IRB Barcelona), Barcelona, Catalonia, Spain; (5) Barcelona Institute of Science and Technology (BIST), Barcelona, Catalonia, Spain; (6) IDIBAPS-Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Catalonia, Spain; (7) Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Catalonia, Spain"RTP801/REDD1 is a stress-responsive protein overexpressed in neurons of patients with neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. Its main function is to inhibit the mTOR pathway, but, if this inactivation is sustained in time, it has a pro-apoptotic effect in differentiated cells like neurons. Nevertheless, RTP801 might have other functions not yet elucidated. In preliminary proteomic studies from our laboratory, RTP801 was found to interact with HSPC117 and DDX1, two proteins that are part of the tRNA splicing ligase complex, which performs the ligation of the tRNA fragments generated during splicing. Since alterations in tRNA metabolism have recently been associated with the development of some neurodegenerative diseases, we aimed to deeper study the relationship between RTP801 and these tRNA-processing enzymes. Here, we confirm by immunoprecipitation that endogenous RTP801 interacts with the tRNA splicing ligase complex, concretely with DDX1, HSPC117 and CGI-99. We also observe changes in the protein levels and cellular distribution of these tRNA-processing enzymes when we knock down RTP801. Additionally, the maturation of intron-containing tRNAs is altered in the cortex of 2-month-old RTP801 knockout mice compared to wild-type. Finally, we also observe related alterations in hippocampal postmortem samples from patients with Alzheimer's disease, where RTP801 is involved in the pathogenesis. These results suggest a novel role of RTP801 in tRNA processing, which must be further studied, as RTP801 could be a potential target to prevent altered tRNA metabolism in neurodegenerative diseases."

40 Is RTP801/REDD1 involved in tRNA processing?

Authors: Campoy Campos, Genís (1,2,3); Torres, Adrián Gabriel (4,5); Solana-Balaguer, Julia (1,2,3); Pérez-Sisqués, Leticia (1,2,3); Alberch, Jordi (1,2,3,6); Pérez-Navarro, Esther (1,2,3,6); Ribas de Pouplana, Lluis (4,5,7); Malagelada, Cristina (1,2,3) Affiliation: (1) Universitat de Barcelona, Facultat de Medicina i Ciències de la Salut, Unitat de Bioquímica, Barcelona, Catalonia, Spain; (2) Institut de Neurociències, Barcelona, Catalonia, Spain; (3) Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain; (4) Institut de Recerca Biomèdica (IRB Barcelona), Barcelona, Catalonia, Spain; (5) Barcelona Institute of Science and Technology (BIST), Barcelona, Catalonia, Spain; (6) IDIBAPS-Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Catalonia, Spain; (7) Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Catalonia, Spain

Abstract: "RTP801/REDD1 is a stress-responsive protein overexpressed in neurons of patients with neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases. Its main function is to inhibit the mTOR pathway, but, if this inactivation is sustained in time, it has a pro-apoptotic effect in differentiated cells like neurons. Nevertheless, RTP801 might have other functions not yet elucidated. In preliminary proteomic studies from our laboratory, RTP801 was found to interact with HSPC117 and DDX1, two proteins that are part of the tRNA splicing ligase complex, which performs the ligation of the tRNA fragments generated during splicing. Since alterations in tRNA metabolism have recently been associated with the development of some neurodegenerative diseases, we aimed to deeper study the relationship between RTP801 and these tRNA-processing enzymes. Here, we confirm by immunoprecipitation that endogenous RTP801 interacts with the tRNA splicing ligase complex, concretely with DDX1, HSPC117 and CGI-99. We also observe changes in the protein levels and cellular distribution of these tRNA-processing enzymes when we knock down RTP801. Additionally, the maturation of intron-containing tRNAs is altered in the cortex of 2-month-old RTP801 knockout mice compared to wild-type. Finally, we also observe related alterations in hippocampal postmortem samples from patients with Alzheimer's disease, where RTP801 is involved in the pathogenesis. These results suggest a novel role of RTP801 in tRNA processing, which must be further studied, as RTP801 could be a potential target to prevent altered tRNA metabolism in neurodegenerative diseases."

41 The ADORA1 mutation linked to early-onset Parkinson's Disease alters adenosine A1-A2A receptor heteromers formation and function

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Abstract: Adenosine is an endogenous autacoid purine nucleoside involved in several physiological functions. In the brain, it modulates neurotransmission through inhibitory adenosine A1 receptors (A1Rs) and stimulatory A2A receptors (A2ARs). These G protein-coupled ARs are involved in motor function and related to neurodegenerative diseases such as Parkinson's disease (PD). In line with this, a recent study associated a new autosomal recessive mutation (G279S) within the A1R gene to the development of early onset PD. Here, we aimed at investigating the impact of this mutation on receptors' structure and function. Our results revealed that the G279S A1R mutation does not alter receptor's ligand binding, constitutive activity or coupling to transducer proteins (i.e., G i and G q) in transfected cells. However, G279S mutation reduced A1R-A2AR heteromer formation and abolished the heteromer-dependent ligand-independent modulation that A1R exerts over the constitutive and agonist-induced activation of the A2AR. Interestingly, computational studies supported that the G279S A1R mutation could have a negative effect on the heterodimer interface stability. Overall, our results indicate that G279S mutation does not modify A1R canonical signalling, whereas it reduces the ability of A1R to act as a negative allosteric modulator of A2AR function.

42 GPR37 N-terminal domain processing defines autaptic receptor signaling.

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Abstract: "G protein-coupled receptor 37 (GPR37) is an orphan receptor that is involved in the juvenile form of Parkinson's disease (PD). The N-terminus of the receptor (i.e. ecto-GPR37) is subject to metalloproteinase-mediated proteolysis, which leads to several receptor forms at the cell surface. PD patients have increased amounts of ecto-GPR37 peptides in the cerebrospinal fluid and an increased expression of GPR37 cleaved isoforms in the brain. Here, we aimed at investigating the impact of ecto-GPR37 on receptor's functionality. To this end, we used the GPR37 full length (FL) and generated five GPR37 N-terminally truncated constructs based on the receptor isoforms identified in human brain samples: Δ1-171 (T1), Δ1-199 (T2), Δ1-219 (T3), Δ1-247 (T4). Next, we assessed their constitutive activity in HEK293T cells and generated an hypothesis about the GPR37 mechanism of action."

43 Setting up CSF a-SYN RT-QuIC, a new diagnostic tool for Parkinson's disease: from the experimental to the routine lab

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Abstract: "Introduction: Differential diagnosis between Parkinson's disease (PD) and atypical parkinsonisms (APs: multiple system atrophy[MSA], progressive supranuclear palsy[PSP], corticobasal degeneration[CBD]) remains chal- lenging. Lately, cerebrospinal fluid (CSF) studies of neurofilament light-chain (NFL) and RT-QuIC of alpha-synuclein (-SYN) have shown promise. Objective: To assess the separate and the combined diagnostic ability of CSF RT-QuIC -SYN and CSF NFL in degenerative parkinsonisms;
Methods: Between 2018 and 2021 we have set up RT-QuIC for -SYN at our lab and here we report an extension of our recently published study (Compta et al., Park Rel Dis 2022; DOI: 10.1016/j.parkreldis.2022.05.006). We collected demographic and clinical data and set up -SYN RT-QuIC at our lab in a cross-sectional cohort of 136 participants: 23 control subjects (CSs), 21 participants with PD, 37 subjects MSA, 33 with PSP, and 22 with CBD. We also determined CSF NFL by ELISA in 122 of the participants: 20 CSs, 18 PD, 32 MSA, 30 PSP, 22 CBD. Results: The sex distribution was 13 women in CS group (56%), 12 in PD (57%), 17 in MSA (46%), 12 in PSP (36%), and 17 in CBD (77%) resulting in significant differences due to more men in PSP and more women in CBD (p= 0.044). There were also significant differences in age driven by younger age in MSA compared to similarly older age in CS, PD, PSP and CBD (p= 0.000038). In terms of the CSF biomarkers, RT-QuIC of -SYN in CSF yielded the following results: all CS were negative (100% specificity for PD vs. CS), 76% of PD were positive (76% sensitivity for PD), 91% for both PSP and CBD were negative (91% specificity for PD vs. tauopathies), whereas in MSA only 11% were positive despite this condition also being a synucleinopathy. Regarding CSF NFL levels, all the APs groups (be it MSA, PSP or CBD) had significantly higher CSF levels of NFL compared to CS and PD (p= 6e-14). ROC curve analyses for increased CSF NFL as a biomarker of APs vs. PD and CS yielded an AUC= 0.91 (95%CI= 0.84-0.98; p= 1e-13) with the optimal cut-off being 1302.83pg/mL (sensitivity= 88%; specificity= 90%). ROC curve analysis combining CSF -SYN RT-QuIC and CSF NFL dichotomized according to the calculated cut-off yielded a greater AUC (0.89; 95%CI= 0.79-0.99; p= 8e-8) than ROC curve analyses with CSF -SYN RT-QuIC (AUC= 0.82; 95%CI 0.70-0.94, p= 0.000007) and CSF NFL (AUC= 0.84; 95%CI= 0.73-0.95; p= 0.00003) separately. Despite differences in sex and age, CSF -SYN RT-QuIC and CSF NFL did not differ between women and men in the entire cohort (p= 0.52 and 0.46, respectively) and there were not differences in age for these biomarkers either (p= 0.06 and 0.70, respectively). Conclusions: The combination of CSF RT-QuIC -SYN and CSF NFL shows high discriminant ability across all groups. Due to the successful implementation of a-SYN RT-QuIC at our experimental lab this test is now available as a routine clinical diagnostic test at the diagnostic laboratory of our hospital."

44 Whole-brain functional connectivity in Parkinson's disease with RBD through threshold-free network-based statistics

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Abstract: Background: threshold-free network-based statistics (TFNBS) is an innovative approach for statistical inference in brain graphs (1). This approach combines threshold-free cluster enhancement and network-based statistic (NBS), methods commonly used in voxel-wise statistical inference and for statistical analysis of brain graphs, respectively (1). It has been applied in different populations to characterize brain functional and structural connectivity, such as in Parkinson's Disease (PD) (1), idiopathic REM sleep behavior disorder (2) or progressive supranuclear palsy (PSP) (3). A relevant objective in translational research is to characterize clinical subtypes of neurodegenerative diseases. In this context, PD with REM sleep behavior disorder is a clinical subtype previously associated with severe cognitive impairment (4) and brain atrophy (5). TFNBS would allow us to characterize, for the first time, the whole-brain resting-state functional connectivity of PD patients with RBD symptomatology. Aim: To characterize functional connectivity through TFNBS in treated PD patients with probable RBD. Methods: The analyzed sample from the Unitat de Parkinson i Trastorns del Moviment (Hospital Clínic de Barcelona, Catalunya) consisted of 27 PD with probable RBD (PD-pRBD; 85.2% males, 68.8 y/o, 11.4 yrs. of education, and 8.6 yrs. of disease duration on avg.) and 32 PD without probable RBD patients (PD-non pRBD; 65.6% males, 64.5 y/o, 12.8 yrs. of education, and 6.3 yrs. of disease duration on avg.), classified using the Innsbruck RBD Inventory (4); and 30 healthy controls (67.5 y/o and 11.4 yrs. of education on avg.). There were no differences between disease groups in medication and disease severity. Sex, motion parameters, and disease duration were introduced as covariates in the analyses when required. TFNBS was used to characterize resting-state interregional functional connectivity in PD-pRBD. Then, in the group of PD-pRBD patients, we explored the association between functional connectivity characteristics and cognitive impairment. Results: PD-pRBD patients showed reduced functional connectivity compared with healthy controls involving cingulate regions with temporal, frontal, insular, and thalamic regions (P-value < 0.001). Moreover, PD-pRBD patients showed reduced functional connectivity between the right ventral posterior cingulate and left medial precuneus compared with PD-non pRBD (P-value < 0.05). The mean connectivity strength from the reduced connections of the PD-pRBD patients compared with the healthy controls correlated with facial recognition impairment. Conclusion: This work demonstrates the existence of disrupted functional connectivity in PD-pRBD, which supports its consideration as a severe PD subtype. The altered posterior connection in PD-pRBD and previous evidence of disrupted posterior functional connectivity in idiopathic RBD (2) suggest that the posterior connectivity alteration may be characteristic along the synucleinopathies spectrum.

45 Cognitive impairment associated with white matter volume reduction and phenylalanine levels in adult phenylketonuria patients

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Abstract: Background and Objective: Phenylketonuria (PKU) has been described as an autosomal recessive disorder of metabolism characterised by increased concentrations of phenylalanine (Phe) in the blood due to the malfunctioning of the hepatic enzyme phenylalanine hydroxylase (PAH). Although an early and continued dietary treatment since birth could prevent most of the brain-related complications, untreated patients experience severe intellectual impairment, behavioural problems, and neurological damage. The aim of the present study is to investigate neuropsychological performance and possible structural brain abnormalities in treated adult PKU patients, as well as its rela-

tionship with disease control measured by blood Phe levels. Participants and Methods: Twenty-two adult PKU patients and 12 healthy controls (HC) underwent comprehensive neuropsychological assessment and T1-weighted magnetic resonance imaging data obtained with a 3T scanner. FreeSurfer (v.7.1) was used to obtain global volumetric measures (cortical and subcortical grey matter and white matter). Sociodemographic, neuropsychological, volumetric and clinical data were analysed using IBM SPSS, p<0.05Neuropsychological impairment in the PKU group was defined as Z-scores below 1.5 according to normative data for each test. Results: Thirty per cent of patients showed cognitive impairment in the full-scale IQ of the WAIS-IV, 20% in the Verbal Comprehension Index of the WAIS-IV, 36.4% in the Perceptual Reasoning Index of the WAIS-IV, 54.5% in the Working Memory Index of the WAIS-IV, 36.4% in the Processing Speed Index of the WAIS-IV, 50% in the Trail Making Test A (TMT-A), 40.9% in the Trail Making Test B, 31,8% in the total of the Rey-Auditory Verbal Learning Test, 13.6% in the delayed recall of the Rey-Auditory Verbal Learning Test, 18.2% in the copy of the Rey-Osterrieth Complex Figure (ROCF) and 22.7% in the immediate recall of the ROCF. Significant negative correlations were found between Blood Phe levels and neuropsychological performance. There were no differences in age (Z=1,309; p=0,065), sex (2=2,941; p=0,086) or education (Z=-1,050; p=0,294) between adult PKU patients and HC. Adult PKU patients showed a significant lower volume in the cerebral white matter (U=39.000; p=0.002) in comparison with HC. Conclusions: Treated adult PKU patients showed variable cognitive outcomes with a higher proportion of impairment in working memory, which was associated with white matter volume reduction. Cognitive performance in treated adult PKU patients was not only associated to structural brain abnormalities but also with disease control at the time of the assessment.

46 Unraveling the dynamics of GPR37-D2R receptor assemblies for the study of the psychotic-related symptoms

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Abstract: The incidence of Schizophrenia corresponds about 1 out of 300 people worldwide, being a disease with considerable repercussion and impact. It is estimated that 1% of the adult population in USA and Europe suffer from this psychiatric disorder. Symptoms are usually classified into two categories: i) Positive ones, mainly characterized by hallucinations and delusions; and ii) negative ones, primarily characterized by the lack of emotional expression and social isolation. The leading hypotheses regarding this disorder are diverse, mainly involving the role and interactions of different neurochemical systems (i.e dopaminergic, serotoninergic, adenosinergic, etc). The decompensated dysregulation systems hypothesis is considered the most widely accepted by the scientific community. The hypothesis states that the etiology of those disorders strongly depend on the interactions of two main neurotransmission systems (i.e. dopaminergic hyperactivation and glutamatergic dysregulations). However, emerging evidence strongly suggests the participation of other neurochemical systems. One of those is the adrenergic system, which demonstrated to have a notable impact on the interaction with the dopaminergic system, thus regulating it. Therefore, one of the key points may be to decipher the dynamics of the interactions between adenosine and dopamine receptors in the context of those psychiatric disorders. Previous studies seem to indicate a decrease in dopaminergic hyperactivation through the A2AR-D2R heterodimer formation, which is related with decrease of the psychotic phenotype. Coherently, A2AR is considered a pharmacological therapeutic target, used to investigate the treatment some neurodegenerative diseases certainly linked with dopaminergic dysregulations, such as Parkinson's Disease (PD). Additionally, in the last decades, the orphan receptor GPR37 has increased its importance in relation to certain types of pathologies with a common neurochemical basis. As an example, it is related to PD, where it can be found in the so-called Lewy Bodies. Recent data and novel studies suggest a potential interaction between the GPR37 and the A2AR-D2R heteromer. Although, the exhaustive knowledge of that interaction is still unknown.

Nevertheless, trying to identify macromolecular targets susceptible to being modulated with drugs could be considered a priority. The postulated GPR37-D2R interaction could potentially modulate decompensated neurochemical systems in schizophrenia trough an amelioration of psychotic symptoms and improving the quality of life of many patients. The following preliminary results show a potential interaction between D2 and GPR37 receptor, in which the latter decreases the doses-response curves with respect to other previous described interactions with the former. Therefore, due to the possible role of GPR37 described in previously studies, this orphan receptor could be a key link in the physiopathology of psychotic-like symptoms found in Schizophrenic patients.
47 Phospho-RNA-seq method discloses higher diversity of sRNAs profiles in SEC-derived plasma subfractionsAutors: Solaguren-Beascoa M (1), Gámez-Valero A (1), Escaramís G (1,2), Ortiz AM (3), Minguet C (3), Costa M (3), Martí E (1,2) Affiliation: (1) Department of Biomedicine, Faculty of Medicine, Institute of Neurosciences, University of Barcelona, C/ Casanova 143 (08036) Barcelona, Spain (2) Biomedical Research Networking Center for Epidemiology and Public Health (CIBERESP), Spanish Ministry of Science and Innovation, Madrid, Spain (3) Grifols Bioscience Research Group, Grifols, Barcelona, Spain "In recent years, RNA sequencing evolution has allowed to decipher and analyze the complex composition of the human transcriptome in a wide range of contexts. Specifically, the study of extracellular RNA in peripheral blood has opened new avenues in the search of disease and biological biomarkers. Diverse library and sequencing protocols have been described aiming to optimize the discovery of different RNA classes. Here, we intend to determine RNA abundance and diversity after applying the already described phospho-RNA pre-sequencing protocol (+PNK) (Giraldez et al., 2019) in extracellular vesicles in comparison to the standard small RNA sequencing approach (-PNK). To understand the added value of Phospho-RNA-seq, we applied this method to total plasma, and EV- and protein-enriched plasma subfractions. Plasma subfractions were isolated by size-exclusion chromatography (SEC), and sequencing data in PNK- and non-PNK treated RNAs were analyzed using SeqCluster and SeqBuster in-house bioinformatic tools. Most classes of sRNAs displayed an increased detection signal in response to PNK treatment, except miRNAs in all samples and tRNA fragments in EVs and protein-enriched pools. Moreover, this treatment stresses the differential sRNAs profiles in EVs- versus protein-enriched fractions. Overall, these results show that PNK treatment highlights an increased diversity in the sRNAs profiles in total plasma and SEC-derived EVs and protein-enriched pools. Furthermore, this strategy offers more opportunities to obtain complementary information in both plasma compartments."

47 Phospho-RNA-seq method discloses higher diversity of sRNAs profiles in SEC-derived plasma subfractions

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Abstract: "In recent years, RNA sequencing evolution has allowed to decipher and analyze the complex composition of the human transcriptome in a wide range of contexts. Specifically, the study of extracellular RNA in peripheral blood has opened new avenues in the search of disease and biological biomarkers. Diverse library and sequencing protocols have been described aiming to optimize the discovery of different RNA classes. Here, we intend to determine RNA abundance and diversity after applying the already described phospho-RNA pre-sequencing protocol (+PNK) (Giraldez et al., 2019) in extracellular vesicles in comparison to the standard small RNA sequencing approach (-PNK). To understand the added value of Phospho-RNA-seq, we applied this method to total plasma, and EV- and protein-enriched plasma subfractions. Plasma subfractions were isolated by size-exclusion chromatography (SEC), and sequencing data in PNK- and non-PNK treated RNAs were analyzed using SeqCluster and SeqBuster in-house bioinformatic tools. Most classes of sRNAs displayed an increased detection signal in response to PNK treatment, except miRNAs in all samples and tRNA fragments in EVs and protein-enriched pools. Moreover, this treatment stresses the differential sRNAs profiles in EVs- versus protein-enriched fractions. Overall, these results show that PNK treatment highlights an increased diversity in the sRNAs profiles in total plasma and SEC-derived EVs and protein-enriched pools. Furthermore, this strategy offers more opportunities to obtain complementary information in both plasma compartments."

48 Early life stress in Caenorhabditis elegans modulates the transcriptome revealing different adult gene expressions across generations

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Abstract: Stress experienced during the critical perinatal period form permanent, imprinted memories that can persistently alter expression levels of key genes leading to changes in behaviour, molecular response and stress throughout later life, including subsequent generations. Despite some studies in this area, there are still some gaps in our understanding of transgenerational epigenetic inheritance. Here using an experimental paradigm, we show that Caenorhabditis elegans form an imprinted behavioural and cellular defence memory in response to early-life stresses. We demonstrate that exposing newly-born worms to toxic antimycin (AM) promotes aversive behaviour through chemotaxis assays and stimulates hsp-6::GFP expression, which is a toxin-specific cytoprotector. Learned adult defences require memory formation during the L1 larval stage and do not appear to confer increased protection against the toxin. In our study, aversive behaviour was inherited only in the F1 generation after exposure to toxins, but molecular alterations were observed up to the F5 generation. Changes in the gene expression of the chromatin modifier set-25 were observed, as well as the gene expression of hsp-6, skn-1, gst-4 and atfs-1 after 1 exposure to the toxic. Besides, we found differences in lifespan after 1 exposure in the F1 to F3 generations. Moreover, in our RNA-sequencing analysis, we found that the expression of 2,299 genes changes in any of the generations with OP50 treatment. many of these changes were observed in F1, and the gene expression of most of them was decreased compared to the control group. Interestingly, among other epigenetic-related enzymes, we found an increase in the gene expression of set-28, a histone methyltransferase, after exposure to AM in the F1. This finding supports the hypothesis about the relevant role of chromatin modifiers in establishing transgenerational epigenetic inheritance (TEI) memory and resulting in the modulation of pathways related to behaviour and ageing. Therefore, exposure to toxic stresses during the critical period can induce adaptive behavioural and cytoprotective responses and promote changes in health outcomes, demonstrating a wide range of changes that can come about after an early-life stressful experience. These results open a new avenue to clarify the effects of the methyltransferases during TEI after exposure to early life stress.

49 In vivo and in vitro characterization of m6A RNA methylation in age-related cognitive decline and AD models

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Abstract: "N6-methyladenosine (m6A) RNA methylation is now considered as one of the main dynamically reversible epigenetic modifications contributing to the development of neural degeneration. This way, abnormal levels of m6A have been shown to be involved in the regulation of gene expression programs in various neurodegenerative diseases such as Alzheimer's Disease (AD). Its methylation is catalyzed by the combined action of different groups of enzymes including, writers, or methylases, and erasers, or demethylases. Among them, recent research on the pathophysiology of AD has focused its study on METTL3 and FTO, respectively. This study aimed to determine the molecular regulatory mechanism by which m6A methylation levels contribute to age-related cognitive decline and its interaction with early amyloid deposition. Characterization of m6A in both SAMP8 (6-month-old) and 3xTg-AD (12-month-old) mice models was carried out. We provided evidence of both an increase in FTO levels as well as a decrease in METTL3 protein levels in the SAMP8 mouse model, which was consistent with the group's previous research on human AD brains. Furthermore, we characterized m6A levels in SH-SY5Y differentiated cells, which showed an increase in cell viability when using a METTL3 activator or instead, an FTO inhibitor. Thus, our results suggest m6A as a novel target for the development of pharmacological drugs. This study was supported by the Ministerio de Economía, Industria y Competitividad (Agencia Estatal de Investigación, AEI) and Fondo Europeo de Desarrollo Regional (MINECO-FEDER) (Projects SAF2015-68749), by the grants PID2020-118127RB-I00 funded by MCIN/AEI/10.13039/501100011033 and by "ERDF A way of making Europe", and 2017SGR106 and 2019LLAV00017 from AGAUR."

50 New HPLC technology for monitoring neurotransmitters in the brain: a pre-clinical approach for neurological disorders

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Abstract:"Background: Noradrenaline, adrenaline, dopamine and serotonin are essential neurotransmitters for normal neuronal function. While noradrenaline is involved in cognitive processes after mental stimulation and novel events, dopamine is associated with cognitive function and serotonin is relevant to synaptic plasticity regulation, neurogenesis and neuronal survival. However, neurotransmitter homeostasis is compromised by aging and neurological diseases such as Alzheimer's disease and depression. Therapeutic monitoring of neurotransmitters and their metabolites, namely dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), presents high relevance particularly to assess disease severity and progression. This work aimed to develop and validate a High-Performance Liquid Chromatography (HPLC) method to accurately quantify noradrenaline, adrenaline, dopamine, DOPAC, HVA and serotonin in mouse brain, resorting to the native fluorescence emitted by the compounds. Materials and Methods: Stock solutions of noradrenaline, adrenaline, DOPAC, dopamine, HVA and serotonin were prepared in perchloric acid 0.4% (v/v) at a concentration of 0.5 mg/mL and diluted with perchloric acid 0.2% (v/v) to prepare the calibration standards and quality control (QC) samples. 4-(Aminomethyl)benzene-1,2-diol was selected as internal standard (IS). For sample preparation, brain tissue was homogenized in ice-cold 0.2 M perchloric acid, and the supernatant was collected after centrifugation. To 100µL of brain homogenate, 10µL of IS were added, followed by protein precipitation with 20µL of 2.0 M perchloric acid. The supernatant (10µL) was then injected into the HPLC. The chromatographic analysis was performed in a Shimadzu HPLC system coupled to a fluorescence detector set at 279 nm (excitation) and 320 nm (emission). Chromatographic separation was achieved on a Grace Apollo C18 chromatographic column (250 x 4.6mm, 5µm). The mobile phase was constituted by methanol and acetate buffer (pH 4.4), constituted by anhydrous sodium acetate (0.1 M), EDTA (0.3 mM), octane sulfonic acid sodium salt (0.5 mM) and acetic acid (0.05 M). The chromatographic column was maintained at 25 C and the mobile phase was pumped at a flow rate of 1.0 mL/min with gradient elution, during a total run time of 23 min. Results and Discussion: Neurotransmitters are endogenous compounds constitutively present in the brain; their values vary according to age, pathological state and other factors. Therefore, to validate the proposed methodology, the endogenous background concentrations of each neurotransmitter were subtracted from the concentrations of the added standards to construct calibration curve and QC. The calibration curves range was defined as follows: noradrenaline (10-400 ng/mL); adrenaline (10-200 ng/mL); DOPAC (50-300 ng/mL); dopamine (10-800 ng/mL); HVA (55-300 ng/mL) and serotonin (35-300 ng/mL). Intra and inter-day accuracy and precision were evaluated for five consecutive days to ensure reproducibility. The method was successfully validated with a recovery higher than 65% for all neurotransmitters. Conclusions: This work presents an innovative HPLC method, validated according to the ICH guideline for bioanalytical method validation. The present method allows the simultaneous quantification of four neurotransmitters and two metabolites in mouse brain homogenates. As major advantage, it resorts to native fluorescence, avoiding unspecific detections. Lastly, it enables an easy sample preparation, thereby saving time and resources, with potential future application in in vivo studies."

51 Epigallocatechin-3-gallate as a new neuroprotective agent against toxicity caused by polymyxins

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Abstract: "Background and Objectives: The appearance of drug-resistant bacteria has made necessary the reintroduction of old antibiotics that were effective but had a narrow therapeutic window. This is the case of polymyxins, a family of old antibiotics that, due to their toxicity, is only used as a last resource against multidrug-resistant gram-negative bacteria. Recent studies have demonstrated that polymyxin-induced toxicity appears to be mediated by the generation of reactive oxygen species. Hence, the administration of epigallocatechin-3-gallate, a component of green tea known for its anti-inflammatory and antioxidant properties, could alleviate polymyxin-induced toxicity and increase its therapeutic window. This study aims to investigate the neuroprotective effects of epigallocatechin-3-gallate on polymyxin-induced neurotoxicity using two in vitro models and an in vivo study. Methodology: Neuroprotection of epigallocatechin-3-gallate against polymyxin-induced toxicity was first studied in two in vitro models. On the one hand, primary neuronal cells were pre-exposed for 2 h to epigallocatechin-3-gallate followed by a 24 h incubation with polymyxin. Then viability of the cells was assessed by an MTT test. On the other hand, zebrafish embryos were exposed from 2-6 h post-fertilization (hpf) to epigallocatechin-3-gallate and kept until 72 hpf with polymyxin when the neurotoxicity was evaluated with a touch-evoked response assay. To better extrapolate the results in vitro to a clinically relevant scenario, an in vivo study with C57BL/6 mice was performed. Animals were administrated for one week with epigallocatechin-3-gallate followed by a 14-day administration with polymyxin. Behavioral tests were performed, and brains were collected and preserved for immunohistochemistry. Results: We have identified that a pre-exposure of epigallocatechin-3-gallate can protect against polymyxin-induced neurotoxicity in primary neuronal cell culture and in the zebrafish embryo model. Moreover, epigallocatechin-3-gallate reduces polymyxin-induced neuroinflammation in mice. Conclusion: The pre-administration of epigallocatechin-3-gallate seems to be a good neuroprotective therapy against polymyxin-induced neurotoxicity. However, more studies to determine the mechanism of protection should be performed."

52 Murine PAS granules and human Corpora amylacea are located in equivalent brain areas

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Abstract: "Corpora amylacea (CA) of human brain are granular bodies formed by polyglucosan aggregates that gather waste products of different origins. Their presence is increased with age and in neurodegenerative diseases. These CA are generated by astrocytes, are released to the cerebrospinal fluid (CSF), and follow an exit route from the brain to the lymphatic system, where they would

be eliminated. In several mouse strains, degenerative granular structures, frequently referred to as "PAS granules" due to their positive staining with periodic acid-Schiff (PAS), have been identified and postulated to be analogous to human CA. Provided PAS granules also appear with aging, the senescence-accelerated mouse prone 8 (SAMP8) strain of mice is a good model to study these granules. In this study we determined the precise localization of PAS granules in the mouse brain of SAMP8 animals in order to determine if these granules, as CA, are located in areas that function as a brain exit doors to the CSF. PAS staining has been used to recognize PAS granules, and immunohistochemistry assays with natural IgMs have been used to detect the neo-epitopes present in PAS granules and to confirm their presence. In addition, immunohistochemistry assays with confocal imaging and 3-D reconstruction have been used. We found that PAS granules are specifically located in the perivascular space (associated to the walls of large blood vessels), in the ventricular zones (in the lateral and the central ventricles) and in subpial areas (within the meninges). This is the first study that demonstrates that PAS granules are located in areas that function as a brain exit doors to the CSF. It also suggest that PAS granules may exit the brain through similar routes than CA, and supports the fact that these granules are the murine equivalent of human CA. Keywords: PAS granules, SAMP8, aging, animal models, immunohistochemistry, IgM staining, PAS staining"

53 Detecting tau in wasteosomes (corpora amylacea) of human brain

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Abstract: Corpora amylacea, recently renamed as wasteosomes, are polyglucosan bodies that appear in the human brain during aging and some neurodegenerative conditions. They collect waste substances and are part of a brain cleaning mechanism. For decades, studies on their composition have produced inconsistent results and the presence of tau protein in them has been controversial. In this work, we reanalyzed the presence of this protein. We first point out a methodological problem in the immunolabeling of these structures. It is well known that to observe tau it is necessary to perform an antigen retrieval. However, in the case of wasteosomes, an excessive antigen retrieval with boiling dissolves their polyglucosan structure, releases the entrapped proteins and, thus, prevents their detection. After performing an adequate pre-treatment, with an intermediate time of boiling, we observed that some wasteosomes from patients with Alzheimer's disease (AD) contained tau, while we did not detect tau protein on those from non-AD patients. These observations pointed the different composition of wasteosomes in different patients and reinforce the role of wasteosomes as waste containers.

54 Renin-Angiotensin System acting drugs: a possible role in Alzheimer's disease?

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Abstract: "Background: Even though approximately 50 million people worldwide have Alzheimer's disease (AD), its cure remains today an unmet clinical need and several efforts are being done to attain it. The attrition rate of research and development (R&D) programs for AD is considerably high probably because the majority of the chemical entities mainly focus on one of the pharmacological targets underlying AD. Renin-Angiotensin System (RAS) acting drugs are evidencing a high potential to delay AD development, in hypertensive patients. Therefore, repurposing RAS drugs for the treatment of AD may be a good attempt to decrease this failure risk. In this context, the present work aimed to evaluate the effect of four RAS drugs (losartan, irbesartan, valsartan and enalaprilat) in relevant AD hallmarks: 1) neuroprotection in two mouse neuronal cell lines, Wild type (N2a-wt) or cells overexpressing human APP (amyloid precursor protein) with Swedish mutation (N2a-APPswe) and 2) on neuroinflammation in BV-2 cells exposed to lipopolysaccharide (LPS). Material and methods: N2a-wt, N2a-APPswe and BV-2 were cultured and treated with 100 μM of each drug and Western Blot was performed to analyze the phosphorylation of protein kinase B (AKT), glycogen synthase kinase 3 beta (GSK3) and the protein levels of heme oxygenase 1 (HMOX1), in N2a-wt and N2a-APPswe cell lines. Moreover, the potential of drugs to mitigate neuroinflammation was investigated in LPS-stimulated microglia through measurement of inducible nitric oxide synthase (iNOS) and pro-interleukin (IL)-1 levels. Additionally, nitric oxide (NO) production was also evaluated. Results: Regarding the neuroprotective effect, irbesartan and enalaprilat significantly increased the phosphorylation of AKT ($p<0.05$). Although not significantly, losartan and valsartan also increased AKT phosphorylation. Additionally, losartan was able to rise the phosphorylation of GSK3 ($p<0.05$). Irbesartan and enalaprilat raised p-GSK3 levels but without significance. As for HMOX1, only irbesartan significantly increased its levels ($p<0.05$). Finally, all tested drugs significantly reduced the levels of iNOS ($p=0.0006$, $p=0.0026$, $p<0.0001$, $p=0.0067$ for valsartan, losartan, irbesartan and enalaprilat, respectively) and NO triggered by LPS in microglia ($p= 0.0003$ for valsartan and enalaprilat, $p< 0.0001$ for losartan and irbesartan). Losartan was also able to significantly reduce pro-IL1 levels ($p= 0.0001$) as well as enalaprilat although not significantly. Discussion: Two main pathological features of AD were addressed in this study: neuroprotection by modulation of the AKT/GSK3 pathway and HMOX1 protein levels; and neuroinflammation by inhibition of iNOS, NO and pro-IL production. In agreement, these results showed that RAS drugs are able to induce the phosphorylation of AKT and GSK3 , inhibiting therefore the deleterious effects of GSK3 that has revealed an important role in the pathogenesis of AD. Moreover, HMOX1, which is antioxidant and anti-inflammatory, was also elevated after treatment with irbesartan in N2a-APPswe. Moreover, an anti-inflammatory activity of RAS drugs was also demonstrated, since losartan was able to decrease pro-IL1 production and all of them decreased iNOS and NO levels in LPS-stimulated microglia, reinforcing their beneficial role in AD. Conclusion: RAS acting drugs demonstrated to modulate in vitro critical pathways involved in neuroinflammation and neuroprotection, supporting their potential as new therapeutic strategies for AD."

55 Licochalcone a reduces neuroinflammation induced by lipopolysaccharide, preventing associated cognitive alterations

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Abstract: "The development of systemic inflammatory stages has been related to the cognitive dysfunction of neurodegenerative diseases, highlighting inflammation as a potential target to prevent neurodegeneration. Particularly, Licochalcone A (LCA) has been described as an emergent drug which has shown multiple therapeutical properties, such as an anti-inflammatory effect. Therefore, it could have a potential preventive effect on neurodegeneration. To our knowledge, little is known about the mechanism underlying LCA's neuroprotective effect. At the same time, no effective treatment able to stop the neurodegeneration has been found yet. Therefore, this study aims to demonstrate the role of inflammation in cognitive decline and the promising preventive effect of LCA in a neuroinflammation mice model, induced by Lipopolysaccharide (LPS).
To perform this study, C57/BL6 six-week-old male mice were intraperitoneally treated with 15 mg/kg/day of LCA 3 times per week during two weeks. Additionally, the last day of treatment the subjects received a final LPS injection of 1 mg/kg, 24 hours before sacrifice. Therefore, mice were divided into 4 different experimental groups, classified in mice treated with saline or LCA and receiving or not the last LPS injection. Before euthanize, long term memory and depression were evaluated by Novel Object Recognition test and Forced Swimming test, respectively. Afterwards, the presence of neuroinflammation was determinated by immunohistochemistry assays and the expression of proteins related to inflammation and cognitive decline were analysed in hippocampus through Western Blot.
The present data report a beneficial effect of LCA by preventing depression and memory loss induced by LPS administration by conferring neuroprotection against neuroinflammation after a previous LCA treatment. This beneficial effect is also correlated to an amelioration of the synapsis dysfunction when a LCA treatment is performed previous to LPS exposure. All together contribute to the maintenance of cognition avoiding the development of neurodegenerative processes.
In conclusion, our results demonstrate the preventive role of LCA treatment against LPS-induced cognitive decline by reducing inflammation and improving synapsis related mechanisms. All this data highlights the potential preventive role of LCA against neurological disorders related where inflammation plays a key role."

56 "Rhein-huprine: a new hybrid drug for the treatment of neurodegenerative diseases"

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Abstract: "Rhein-Huprine (RHE-HUP) is -secretase (BACE-1) and acetylcholinesterase (AChE) inhibitor, two of the most important factors involved in Alzheimer's Disease (AD), making this drug a new potential candidate for the treatment of AD. Moreover, an increasing number of studies indicate linkage between type 2 diabetes mellitus (T2DM) and AD, showing that both diseases share some common pathophysiological features, to the point of knowing AD as type 3 diabetes mellitus. In fact, BACE inhibitors have been successfully used in different studies for the treatment of T2DM. Therefore, dual therapy that targets pathways of both diseases could be regarded as a beneficial approach. In the present work, we aimed to demonstrate the efficiency of this compound when, in addition to the AD pathology, there is an exposure to a high-fat diet (HFD). To carry out this study, APPswe/PS1dE9 (APP/PS1) female mice of 6-months-old fed with HFD were used. For that, animals were fed with conventional chow or with HFD, from their weaning until their sacrifice, at 6 months. At the age of 5 months, animals were treated either saline or RHE-HUP intraperitoneally three times per week for one month. Before sacrifice, behavioral tests were performed to determine cognitive decline. Moreover, other techniques such as immunofluorescence, ELISA assay and GolgiStain Kit were carried out to analyze different hallmarks in AD. Our results showed an improvement of cognitive decline accompanied by a decrease in -amyloid accumulation and A 42 peptide load after RHE-HUP treatment. In addition, a reduction in the inflammatory response and a recovery in the number of dendritic spines were observed in this group. Taken all together, evidence suggests that RHE-HUP could be a new candidate for the treatment of AD, even for those patients who have a major risk factor such as T2DM, due to its multi-target profile which allows for the improvement of some of the most important hallmarks of the disease."

57 Age-and sex-dependent changes in the cerebrospinal fluid proteome in a transgenic rat model of Alzheimer's disease

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Abstract:"Background: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder in the elderly. Because currently there is no effective treatment or prevention for AD, identification of AD fluid biomarkers in the neuropathological progression of the illness is crucial to clinical practice and therapeutic trial design in patients and animal models. Here we analyzed the CSF proteome in the TgF344-AD rat model that recapitulate the full spectrum of Alzheimer's disease neuropathology (Cohen et al., 2013). Methods: A total of 60 validated samples from male and female TgF344-AD rats and non-transgenic littermates at 4, 10'5 and 16'5 months (n=5/group) were selected for the study. Proteomic analyses were performed in the CRG/UPF Proteomics Unit (Barcelona, Spain) and peptide data was analyzed by MSqRob Shiny App, using Variance Stabilizing Normalization. Protein fold-changes and their corresponding adjusted p-values were obtained performing the Standard statistical test. Functional enrichment analyses were performed using PANTHER and PathfindR tools. Results: Peptide quantification data of the CSF proteome, retrieved from Proteome Discoverer, matched to a total of 1802 proteins. From these results, we obtained a significant number of protein changes during the course of rat pathology, even prior to A deposition (4 months). However, a greater number of deviations were found at later stages of the disease, especially in males. Noteworthy, synaptic proteins were particularly altered at 16'5 months, although some changes were already evidenced before A plaques. According to PANTHER and PathfindR, biological pathways involved in glia-neuron communication, neuronal assembly, memory or neuroinflammation were altered in this rat model, to a certain degree comparable to human neuropathology. Conclusions: This study provides a comprehensive analysis of the age-and sex-dependent changes in the CSF proteome in TgF344-AD animals. These findings support the use of the CSF proteome in the TgF344-AD rat model to monitor disease progression and for pre-clinical AD research."

58 Knockout of GADD45 alters cognition, dendritic branching and axonal morphology of neurons in mice.

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Abstract: "Growth arrest DNA damage-inducible protein (GADD45) is implicated in different responses to cell injury, suggesting that this protein may participate in survival mechanisms, including apoptosis, autophagy, cell cycle arrest or DNA repair. Therefore, GADD45 protein is related to aging and life span control, essential for brain function and memory formation. Moreover, its dysfunction or deletion might underlie pathophysiological conditions such as neuropsychiatric disorders, suggesting that it could be a potential therapeutic target in age-related diseases such as Alzheimer Disease (AD). In this study, we used Wild Type (WT, n=15) and GADD45 Knockout (KO, n=15) mice models to evaluate the role of this protein in AD progression. Behavioral tests showed that GADD45 KO mice presented a cognitive impairment compared to WT animals. Molecularly, the lack of GADD45 protein significantly reduced the dendritic spine length of the neurons. Moreover, KO animals showed a significant increase in pro-inflammatory cytokines and Tau pathology features as well as autophagy markers in the brain. These findings demonstrated that the lack of GADD45 protein exacerbates AD pathology, which suggests that this protein might be a potential target to slow down AD progression.
This study was supported by the Ministerio de Economía, Industria y Competitividad (Agencia Estatal de Investigación, AEI) and Fondo Europeo de Desarrollo Regional (MINECO-FEDER) (Projects SAF2015-68749), by the grants PID2020-118127RB-I00 funded by MCIN/AEI/10.13039/501100011033 and by "ERDF A way of making Europe", and 2017SGR106 and 2019LLAV00017 from AGAUR."

59 Gene expression profile during aging in SAMP8 identifies transcripts involved in cognitive decline and Alzheimer's Disease hallmarks

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Abstract: "Background: The senescence-accelerated mouse 8 (SAMP8) represents an ideal model for studying Alzheimer's disease (AD), as they exhibit age-related learning and memory impairments consistent with early onset and rapid progression of senescence. To identify transcriptional changes that occur during the progression of the disease, in this study, we aimed to analyse and compare the gene expression profiles involved in the main molecular pathways involved in neurodegeneration and cognitive impairment in Senescence-accelerated resistant 1 (SAMR1) and SAMP8 mice at 3, 7 and 9 months of age. Methods: A total of 40 female SAMR1 and SAMP8 were randomly divided into the six groups (SAMR1 of 3, 7 and 9 months and SAMP8 mice of 3, 7 and 9 months). A microarray analysis of 22.000 genes was performed, followed by a functional analysis using the Gene Ontology option (NCBI) and the study of altered molecular pathways using the KEGG (Kyoto Encyclopedia of Genes and Genomes). Results: SAMP8 mice exhibited 2,516 dysregulated transcripts at 3 months of age, 2,549 transcripts at 7 months and 2,453 genes at 9 months compared to the SAMR1 mice of the same age. These accounted for 11.3% of the total. The results revealed that with age, there is a ten-

dency to increase gene expression of down-regulated transcripts, and a decrease of those over-expressed. Interestingly, most of these genes were found to be involved in neurodegenerative pathways associated with AD: apoptosis, inflammatory response, oxidative stress and mitochondria. qPCR results indicated that the expression of Ndufs4, Slc25a14, Il-1 , Slc25a14, TST/Rhodanese, Idh3g, Sema6a among others were differently expressed during aging. Conclusions: These results further revealed that significant differences exist in the gene expression profile at different ages between SAMR1 and SAMP8 strains. Importantly, bioinformatic analysis showed a significant alteration in genes involved in age-related cognitive decline including mitochondrial processes. This study was supported by the Ministerio de Economía, Industria y Competitividad (Agencia Estatal de Investigación, AEI) and Fondo Europeo de Desarrollo Regional (MINECO-FEDER) (Projects SAF2015-68749), by the grants PID2020-118127RB-I00 funded by MCIN/AEI/10.13039/501100011033 and by "ERDF A way of making Europe", and 2017SGR106 and 2019LLAV00017 from AGAUR."

60 Implications of Astrocytic RTP801 in Alzheimer's disease

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Abstract: "Neuroinflammation is a key player in many neurodegenerative diseases, including Alzheimer's disease. In this process, astrocytes and microglia are the main cells involved, releasing cytokines, chemokines, prostaglandins, NO, and ROS. The release of these pro-inflammatory molecules has devastating consequences, as it leads to neuronal death, synaptic dysfunction, and inhibition of neurogenesis. The protein RTP801, also called REDD1, has been recently involved in neuroinflammation. RTP801 levels are higher in the hippocampus of AD patients. Such increased levels of neuronal RTP801 correlated with the severity of neurofibrillary tangles distribution, progressive depositions of A , and astrogliosis. This study aims to assess whether astrocytic RTP801 affects memory, anxiety, and neuroinflammation in the AD animal model (5xFAD mice). Silencing astrocytic RTP801 in 5xFAD mice recovered the anxiety-like phenotype at the Plus Maze behavioral test and improved the long-term spatial memory evaluated by the T-maze. The astrocytic silencing of RTP801 in 5xFAD mice also reduced the protein levels of some inflammasome components such as NLRP3, ASC, and pro-caspase-1 in hippocampal samples compared to 5xFAD controls. In vitro, silencing RTP801 with lentiviral particles in primary neuron and astrocyte cultures also reduced NLRP1. Hence, we conclude that astrocytic RTP801 is contributing to neuroinflammation in the pathogenic context of AD both in vitro and in vivo."

61 The Δ9-tetrahydrocannabinol and cannabidiol combination reduces the excessive glutamatergic activity in an animal model of Alzheimer's disease

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Abstract: "Keywords: Alzheimer's disease, cognitive impairment, cannabinoids Alzheimer's disease (AD) is the most common form of dementia and is characterized by a progressive loss of memory and other mental abilities. Current therapies against AD are not totally effective, which highlights the need for new therapeutic strategies. Previous results from our group demonstrated that a combination of non-psychoactive doses of the natural cannabinoids Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), the main components of the first cannabis-based medicine approved in many countries, reduces cognitive decline in a mouse model of AD, the APP/PS1 mice. However, the molecular mechanisms underlying this therapeutic effect are not completely understood. Here, we studied the effects of THC and CBD on the glutamate homeostasis and on synaptic plasticity in the hippocampus of APP/PS1 mice because these two processes are known to be altered in AD. Thus, by using in vivo microdialysis and HPLC techniques, we have quantified the glutamate levels in the hippocampus of wild-type and APP/PS1 animals in response to veratridine and the glutamate transporter-1 inhibitor dihydrokainate (DHK) after a chronic treatment with THC and/or CBD. Interestingly, THC+CBD treatment reduced the veratridine-evoked glutamate release in both genotypes and attenuated the enhanced glutamate levels observed in DHK-treated APP/PS1 mice. In contrast, our results by using ballistic labelling demonstrated that THC+CBD chronic treatment does not significantly impact on dendritic spine density and morphology in the hippocampus of APP/PS1 mice. These results suggest that cognitive improvement after THC+CBD treatment could be related with a reduction of the excitotoxicity occurring in our AD model."

62 Opioid receptors contribute to subanesthetic (S)-ketamine behavioral and analgesic effects

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Abstract: Ketamine, a racemic mixture of (S)-ketamine and (R)-ketamine enantiomers, has been used as an anesthetic, analgesic and more recently, as an antidepressant. However, ketamine has known abuse liability (due to its psychoactive effects) which raises concerns for its therapeutic use. (S)-ketamine was recently approved by the FDA and EMA for treatment-resistant depression. Yet, its mechanism of action remains poorly defined. Ketamine's canonical action at NMDA receptors has been extensively studied, however, its action on other targets remains marginally explored. A preliminary target screen showed that (S)-and (R)-ketamine can bind to opioid receptors (OR). Our in vitro pharmacological studies showed that (S)-ketamine not only binds but also activates mu- and kappa-OR at similar concentrations than the ones required to bind to NMDAR. Intravenous self-administration of (S)-ketamine in rats was blunted by both naltrexone and MK-801, indicating an involvement of both NMDAR and OR on (S)-ketamine rewarding effects. Next, our PET imaging studies showed that acute and chronic (S)-ketamine treatment decreased [18F]DPN binding potential, likely due to a downregulation of mu- OR expression. Finally, by using the hot plate test in mice, we observed that chronic treatment with (S)-ketamine impairs morphine analgesic effects, which is probably due to its ability to modulate mu- OR expression and/or activity. Overall, our in vivo and in vitro studies unravel the complex mechanism of action of ketamine and should help develop safer therapeutic approaches to treat depression and other neuropsychiatric disorders.

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