B·DEBATE International Center for Scientific Debate BARCELONA

Sant Joan de Déu Research Foundation

# CONNECTING THE GROWING BRAIN

## UNDERSTANDING NEUROPAEDIATRIC DISEASES THROUGH SYNAPTIC COMMUNICATION

November, 26th and 27th, 2015

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# B·Debate International Center for Scientific Debate

BARCELONA

**"B·Debate strives to help position Barcelona as a benchmark in generating knowledge and Catalonia as a country of scientific excellence"**

B·Debate is an initiative of Biocat with support from "la Caixa" Foundation which aims to drive top-notch international scientific events to foster debate, collaboration and open exchange of knowledge among experts of renowned national and international prestige. The debates are focused on the integration of diverse disciplines of science in order to tackle major scientific and societal challenges.

# CONNECTING THE GROWING BRAIN

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# WELCOME

Dear Guests and Participants,

It is our pleasure to welcome you to the meeting "Connecting the Growing Brain. Understanding Neuropaediatric Diseases Through Synaptic Communication", co-organized by B·DEBATE (an initiative of Biocat and "la Caixa" Foundation) Hospital Sant Joan de Déu (HSJD, University of Barcelona) and Fundació Sant Joan de Déu (FSJD) with the collaboration of EISAI, and the international networks I-NTD and Connecting the Growing Brain.

The study of the brain and brain diseases is amongst the most complex in human biology. In children, continuous growth and change only add to this inherent complexity. Neurological and psychiatric conditions are very common in paediatrics. It is estimated that they can affect up to 20% of the paediatric population (children and adolescents). Academic tradition classifies diseases according to a collection of symptoms, with reduced focus on pathophysiology. As a consequence, and despite sharing common neurobiological mechanisms, disorders such as epilepsy and neuropsychiatric disorders are considered completely different entities. Therefore an important obstacle that hinders our understanding of the developing brain is the "fragmented" clinical approach which primarily focuses on symptoms rather than on understanding mechanisms and aiming for prevention and cure. On the other hand, only very few neuropaediatricians are trained in basic neuroscience. The very significant dissociation between basic research and clinical practice in these fields has resulted in a long lasting translational research deficit. This has so far been a major impediment for understanding the developing human brain, ultimately precluding the development of new therapeutical strategies.

The synapse is the communication space between cerebral cells. Synaptic connections provide the basis for communication through neurotransmitters, trophic factors and signalling mechanisms. Rare inherited monogenic disorders or the interaction of genetic and environmental factors in prevalent neuropaediatric disorders can alter these biological processes. Disruption in synaptic function during childhood and adolescence can produce symptoms such as severe motor disorders (as infantile parkinsonism), early-onset epilepsy and neuropsychiatric conditions such as ADHD, autism and psychotic disorders.

With the aim to provide an interdisciplinary forum addressed to paediatric neurologists, psychiatrists, basic neuroscientists as well as biomedical professionals involved in different aspects of the developmental brain, the organizers foster a series of debates focused on the idea of changing paradigms and characterize synaptic disfunction in paediatric neurological conditions. Internationally recognized experts will discuss about neurotransmission systems, signaling pathways, brain connectivity patterns and future research in new classifications and treatments in neuropaediatric disorders.

Yours sincerely,

Àngels García-Cazorla and B·DEBATE

# PROGRAM

## Thursday, November, 26th, 2015

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| 9:00 | **Welcome**<br>**Jordi Portabella**, Director of the Area of Science and Knowlegde, "la Caixa" Foundation<br>**Laia Arnal**, Head of Research and Scientific Debate, Biocat<br>**Àngels García-Cazorla**, Coordinator of the Neurometabolic Unit, Hospital Sant Joan de Déu |
| 9:10 | **SESSION 1: SYNAPTIC DETERMINANTS OF NEUROPAEDIATRIC DISORDERS I: A GLOBAL OVERVIEW**<br>Coordinator: **Àlex Bayés**, Biomedical Research Institute Sant Pau, Barcelona, Spain |
| 9:10 | **Synaptic Function and Brain Networks in Childhood**<br>**Sakkubai Naidu**, Kennedy Krieger Institute, Baltimore, USA |
| 9:45 | **Mechanisms of Synaptic Dysfunction in Neuropaediatric Disorders**<br>**Àlex Bayès**, Biomedical Research Institute Sant Pau, Barcelona, Spain |
| 10:20 | **Open Debate** |
| 11:00 | **Coffee Break** |
| 11:30 | **SESSION 2: SYNAPTIC DETERMINANTS OF NEUROPAEDIATRIC DISORDERS II: FOCUSED ON GROUPS OF DISEASES**<br>Coordinator: **Rafael Artuch**, Hospital Sant Joan de Déu, Barcelona, Spain |
| 11:30 | **Synaptic Determinants of Epilepsy in Children**<br>**José Maria Serratosa**, Fundación Jiménez Díaz, Madrid, Spain |
| 12:00 | **Neuroligins at Inhibitory Synapses - from Synaptogenesis to Autism Spectrum Disorders**<br>**Nils Brose**, Max Plank Institute, Göttingen, Germany |
| 12:30 | **Synaptic Determinants of Movement Disorders in Children**<br>**Manju Kurian**, Great Ormond Street Hospital, London, UK |
| 13:00 | **Open Debate** |
| 13:30 | **Lunch** |
| 15:00 | **SESSION 3: SYNAPTIC DETERMINANTS OF NEUROPAEDIATRIC DISORDERS III: FOCUSED ON MAIN GROUP OF MOLECULES INVOLVED IN SYNAPTIC COMMUNICATION**<br>Coordinators: **Àngels García-Cazorla**, Hospital Sant Joan de Déu, Barcelona, Spain<br>**Carles Sindreu**, Universitat de Barcelona, Barcelona, Spain |
| 15:00 | **Neurotransmitter Systems I. Disorders of Monoamines (Dopamine and Serotonin)**<br>**Roser Pons**, University of Athens, Athens, Greece |
| 15:30 | **Neurotransmitter Systems II. Disorders of GABA and Glutamate**<br>**Elisenda Cortès**, Hospital Sant Joan de Déu, Barcelona, Spain<br>**Xavier Altafaj**, Bellvitge Biomedical Research Institute, L'Hospitalet de Llobregat, Spain |
| 16:00 | **Short Break** |
| 16:15 | **Other Molecules Involved in Synaptic Transmission and Disorders in Children**<br>**Sofía Duarte**, Instituto de Medicina Molecular, Lisboa, Portugal |
| 16:45 | **Synaptic Metabolism: a New Approach to Study Neuropaediatric Disorders**<br>**Àngels Garcia-Cazorla**, Hospital Sant Joan de Déu, Barcelona, Spain |

# PROGRAM
## Thursday, November, 26th, 2015

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| 17:15 | **Unraveling Secondary Neurotransmitter Deficiencies in Genetic Disorders**<br>**Gabriella Horvarth**, BC Children's Hospital, Vancouver, Canada |
| 17:45 | **The iNTD Registry: A New Clinical Database of Patients with Inborn Neurotransmitter, Pterin and Folate Disorders**<br>**Thomas Opladen**, Heidelberg University Hospital, Heidelberg, Germany |
| 18:15 | **Open Debate** |
| 19:00 | **Cocktail at CosmoCaixa Museum** |

# PROGRAM
## Friday, November, 27th, 2015

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| 9:00 | **SESSION 4: BIOMARKERS, GENETICS, PROTEOMICS AND METABOLOMICS IN SYNAPTIC DISEASES**<br>Coordinators: **Bru Cormand**, Universitat de Barcelona, Barcelona, Spain<br>**Xavier Altafaj**, Bellvitge Biomedical Research Institute, Spain |
| 9:00 | **Metabolomic and Proteomic of the CSF**<br>**Benoit Colsch**, CEA Atomic Energy and Alternative Energies Commission, Paris, France<br>**Eduard Sabidó**, Centre for Genomic Regulation, Barcelona, Spain |
| 9:30 | **System Biology in Synaptic Disorders (Focused in Rett Syndrome)**<br>**Sakkubai Naidu**, Kennedy Krieger Institute, Baltimore, USA |
| 10:00 | **Genetic Tools Focused on Diagnosis**<br>**Judith Armstrong**, Hospital Sant Joan de Déu, Barcelona, Spain<br>**Lluís Armengol**, qGenomics, Barcelona, Spain |
| 10:30 | **Open Debate** |
| 11:00 | **Coffee Break** |
| 11:30 | **SESSION 5: BRAIN NETWORKS AND CIRCUITRIES**<br>Coordinators: **Vesna Prchkovska**, Mint Labs, Barcelona, Spain<br>**J. Antoni Ramos-Quiroga**, Vall d'Hebron Research Institute, Barcelona, Spain |
| 11:30 | **Connectomics in Neuropaediatric Disorders**<br>**Paulo Rodrigues**, Mint Labs, Barcelona, Spain |
| 12:00 | **Brain Development in Neuropsychiatric Disorders**<br>**J. Antoni Ramos-Quiroga**, Vall d'Hebron Research Institute, Barcelona, Spain |
| 12:30 | **Brain Networks in Neuropsychiatric Disorders in Children**<br>**Xavier Castellanos**, New York University, New York, USA |
| 13:00 | **Open Debate** |
| 13:30 | **Lunch** |

# PROGRAM

## Friday, November, 27th, 2015

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| 15:00 | **SESSION 6: MODELS AND NEW THERAPEUTIC APPROACHES FOR SYNAPTIC DISEASES**<br>Coordinators: **Soledad Alcántara**, Universitat de Barcelona, Barcelona, Spain<br>**Pau Gorostiza**, ICREA – Institute for Bioengineering of Catalonia, Barcelona, Spain |
| 15:00 | **Current Cellular Models of Synaptic Diseases**<br>**Héctor Díez**, Fundació Sant Joan de Déu, Barcelona, Spain |
| 15:20 | **Animal Models of Synaptic Diseases**<br>**Soledad Alcántara**, Universitat de Barcelona, Barcelona, Spain |
| 15:40 | **Pharmacological Approaches for Synaptic Disorders**<br>**Mara Dierssen**, Centre for Genomic Regulation (CRG) and Institut Municipal d'Investigacions Mèdiques (IMIM), Barcelona, Spain |
| 16:00 | **Short Break** |
| 16:15 | **Chaperone Therapy for Synaptic Disorders**<br>**Aurora Martínez**, University of Bergen, Bergen, Norway |
| 16:35 | **Gene Therapy in Synaptic Disorders**<br>**Cristina Fillat**, August Pi i Sunyer Biomedical Research Center (IDIBAPS), Barcelona, Spain |
| 16:55 | **Manipulation of Biological Activity with Light**<br>**Pau Gorostiza**, ICREA – Institute for Bioengineering of Catalonia, Barcelona, Spain |
| 17:15 | **Open Debate** |
| 17:45 | **Closing Remarks and Future: Development of the International Network "Connecting the Growing Brain". By Àngels García-Cazorla** |

# SCIENTIFIC COMMITTEE

**Àngels García-Cazorla**, . Pediatric Neurologist. Coordinator of the Neurometabolic Unit and Principal Investigator of the Synaptic Metabolism Laboratory, **Hospital Sant Joan de Déu**, Barcelona, Spain

She received her M.D. from the University of Barcelona Medical School and obtained a Pediatrics degree and a Ph.D (European Doctorate in mitochondrial diseases) at the "Universitat Autonoma de Barcelona". She did her predoctoral training in inborn errors of metabolism (IEM) at Hôpital Necker, Paris, and a post-doctoral research fellowship in the department of Neurology at Columbia University, New York. She coordinates the Neurometabolic Unit at Hospital Sant Joan de Deu in Barcelona and develops translational research in the field of inborn errors of neurotransmitters and mechanisms of synaptic communication in neurometabolic and rare neurogenetic diseases. She has been granted with 19 grants in metabolic and neurotransmitter disorders and is Associate Professor of Paediatrics at the University of Barcelona. She is currently involved as co-investigator in the international network for the study of neurotransmitters I-NTD (http://www.intd-online.org) and has founded the project "Connecting The Growing Brain" (http://www.connectingthegrowingbrain.com) for the study of synaptic communication in neuropaediatrics. Over the years she has contributed to paediatric neurology and neurometabolism with more than 100 publications.

**Soledad Alcántara**, Associate Professor, Department of Pathology and Experimental Therapeutics, School of Medicine (Bellvitge Campus) **University of Barcelona**, Barcelona, Spain

Graduated in Biological Sciences at the University of Valencia and PhD at the University of Barcelona (UB) in 1995, from 1996 to 2002 she developed her postdoctoral training in various prestigious European and USA Research Centers (INSERM U106, France; Bristol-Mayers Squibbs Pharmaceutical Research Institute, and Scripps Research Institute, USA; etc,), addressing different aspects of the CNS development and regeneration. Since 2003 is the leader the Neural Development Research Group (UB) focused in three main aspects: 1) Identification of BDNF signaling effector genes and their function in cerebral cortex morphogenesis. 2) Regulation of the neurovascular niche during development and its modulation trough metabolic and biomaterial approaches to promote CNS regeneration. 3) Identification of biomarkers in congenital and acquired neuropathology of synaptic development. S. Alcántara has conducted several projects since 1999, is member of the Spanish Society for Neuroscience and of the International Society for Neurochemistry, and has an H-index of 28.

**Rafael Artuch**, Clinical Biochemist, Chair of the Department of Inborn Errors of Metabolism of th Clinical Biochemistry Laboratory, and Group leader of the Unit-703 from CIBERER at the Inborn Errors of Metabolism Unit, **Hospital Sant Joan de Déu**, Barcelona, Spain

Rafael Artuch main domain research is in the field of inborn errors of metabolism (IEM), since he works in a laboratory Hospital, in the first-line diagnosis of these patients. Among IEM, he has focused his attention mainly in 2 fields: in genetic diseases of neurotransmission and in mitochondrial disorders (mainly in CoQ deficiency syndromes) and the research projects in this field in which he has been involved have been funded by public institutions, such as CIBERER, Instituto de Salud Carlos III-FIS and European Union

**Àlex Bayés**, Principal Investigator, **Biomedical Research Institute Sant Pau**, Barcelona, Spain

Àlex Bayés (AB) received his PhD on Biochemistry in 2005 (UAB, Barcelona). His doctoral research turned into several publications including a first author article in PNAS. Afterwards he performed a postdoctoral stay, between 2006 and 2012, at The Sanger Institute (Cambridge, UK) and, briefly, at Edinburgh University (UK) with Professor Seth GN Grant. Since May 2012 AB independently runs his own research laboratory at the Biomedical Research Institute Sant Pau (Barcelona). AB's research aims to understand the molecular mechanisms governing synaptic function. His work addresses the proteomic study of postsynaptic protein complexes found at glutamatergic synapses, particularly the postsynaptic density (PSD), as these supra-molecular structures are key to the reception and integration of excitatory neural signals. His methodology arises from the idea that protein complexes are highly coordinated molecular machines, which have to be understood as a whole system. For this reason AB's research does not aim at understanding the role of a particular synaptic protein or pathway but rather ambitions to understand the organisation and dynamics of the whole postsynaptic proteome and how this governs synaptic function. AB is also interested in investigating how the alteration of the normal molecular function of postsynaptic complexes contributes to brain disorders, particularly to intellectual disabilities (ID). AB recent work has importantly contributed to 2 interrelated and now well-accepted ideas. First, that the postsynaptic proteome has been highly conserved during animal evolution and, second, that mutations in genes predominantly expressed at the postsynapse are involved in many mental and behavioural disorders, specially in ID, autism spectrum disorders (ASD) and schizophrenia.

**Sofía Duarte**, Neurologist, Clinical Researcher, Child Neurology Department, Hospital de Dona Estefânia, CHLC, **Instituto de Medicina Molecular**, Faculdade de Medicina da **Universidade de Lisboa**, Lisboa, Portugal

She received her MD from the Faculty of Medicine at Coimbra University, Portugal. During 2007 she completed the Neuroscience and Behaviour Biology Master from Pablo de Ollavide University, Spain. She became interested in biomedical and translational research during Neurology residence and then decided to become a Neuropediatrics specialist. She integrated the Neurology research laboratory at Hospital San Joan de Déu and developed a research project for the study of epileptic encephalopathies of the first year of life, using a cerebrospinal fluid proteomic approach. In 2011 she was admitted in the Programme for Advanced Medical Education of Calouste Gulbenkian Foundation. She obtained her PhD at Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon. She has been focusing her research on the characterization of synaptic disturbances that underlie neurodevelopmental disorders, in particular Rett Syndrome, Angelman Syndrome and epileptic encephalopathies of the first year of life.

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**Manju Kurian**, Paediatric Neurologist, Department of Neurology, Movement Disorders Unit, **Great Ormond Street Hospital**, London, UK

Dr Manju Kurian is a Wellcome Trust Intermediate Clinical Fellow at UCL-Institute of Child Health. Her research encompasses gene discovery, molecular neuroscience (including the use of patient-derived induced plutipotent cell models) and novel therapeutics for childhood neurological disorders. She is an honorary Consultant Paediatric Neurologist at Great Ormond Street Hospital with expertise in childhood movement disorders.

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**Aurora Martínez**, Professor, Department of Biochemistry, **University of Bergen**, Norway

PhD biochemistry, UPV/EHU (1988); postdoctor (1988-1994) at University of Bergen (UiB), Norway; Associate professor, 1995, and Full professor, 1997 at Department of Biomedicine, UiB. Martinez is the Leader of research group "Biorecognition", Dept. Biomedicine, UiB. Research interests: Development and application of biophysical methods in structural, functional and thermodynamic studies of protein-ligand and protein-membrane interactions. The research at present focuses on translational studies and search of novel therapeutic approaches for activation or inhibition of biomolecular networks of clinical relevance, using isolated proteins, cells and animal models. Special interest on genotype-phenotype correlations and investigation of genetic misfolding diseases, notably phenylketonuria (PKU) and THD. In this field Aurora Martinez has contributed with important publications characterizing molecular mechanisms behind tetrahydrobiopterin responsive PKU and the effect of pharmacological chaperones, which are compounds with therapeutic potential for correction of misfolding diseases. Member of the Norwegian Academy of Sciences and Letters since 2007. Partner of the K.B. Jebsen Center for neuropsychiatric diseases since 2011. President elect of the Norwegian Biochemical Society (2016-).

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**Thomas Opladen**, Consultant for Child Neurology and Inborn Errors of Metabolism, Divsion of Child Neurology and Metabolic Medicine , **University Children Hospital Heidelberg**, Heidelberg, Germany

Thomas Opladen got his Degree in Paediatrics in 2008, he then got specialised in paediatric metabolic medicine in 2009. In 2011 he got specialisation in paediatric intensive care medicine, and in 2015 he got specialization in paediatric neurology. All of them by the University Children's Hospital Heidelberg, in Germany. He completed his *Venia legenid* (Habilitation) in 2014. Since 2014 he is te coordinator of the iNTD network (International Working Group on Neurotransmitter related Disorders), and Consultant for Child Neurology and Inborn Errors of Metabolism.

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**Roser Pons**, Pediatric neurologist Assistant professor, Children's Hospital Agia Sofia, First Department of Pediatrics, **National and Kapodistrian University of Athens**, Athens, Greece

Assistant Professor of Pediatric Neurology at the First Department of pediatrics of the National and Kapodistrian University of Athens. Member of the International working group on neurotransmiter related disorders and member of the Medical and Scientific Advisory Board of the Pediatric Neurotransmiter Disease Association and of the AADC Research trust. She works as pediatric neurologist and movement disorder specialist at the Children's Hospital Agia Sofia where she is involved mainly in patient care of children with complex neurologic disorders including neurometabolic diseases, rare neurologic diseases and also cerebral palsy. She is involved in clinical research that is based on the collaboration with multiple disciplines including genetics, biochemistry, rehabilitation, pathology, neuroradiology and biomechanics. Her main research areas include the genetic basis of rare diseases associated with movement disorders.

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# INVITED SPEAKERS

## Thursday, November, 26th, 2015

**Àlex Bayés**, Principal Investigator, **Biomedical Research Institute Sant Pau**, Barcelona, Spain

(See his CV at the Scientific Committee Section)

Coordinator of the SESSION 1: SYNAPTIC DETERMINANTS OF NEUROPAEDIATRIC DISORDERS I: A GLOBAL OVERVIEW

**Sakkubai Naidu**, Peditrician and Neurologist, **Kennedy Krieger Institute, Baltimore**, USA

SakkuBai Naidu is a trained pediatrician and neurologist with special interest in developmental and neurogenetic disorders affecting children and adults. Combining clinical analysis with technological advances in neuroimaging, genetics and neuroscience, shi is able to accurately characterize neurogenetic disorders. Her activities are at the interface between clinical neurology and basic sciences, providing a unique opportunity to understand the developing brain, the biological basis of disease, and to develop new strategies for prevention and therapy.

**Synaptic Function and Brain Networks in Childhood**

**Àlex Bayés**, Principal Investigator, **Biomedical Research Institute Sant Pau**, Barcelona, Spain

(See his CV at the Scientific Committee Section)

**Mechanisms of Synaptic Dysfunction in Neuropaediatric Disorders**

Human genetic studies have clearly established a very strong connection between genes expressed at the synapse and disorders affecting normal brain and cognitive development. This is particularly the case for proteins with a high expression level at synapses. Molecular and proteomic studies of cellular and animal models of neurodevelopmental disorders have further contributed to the notion that the perturbation of the subtle molecular mechanisms behind synaptic function could importantly contribute to these disorders. In this lecture we aim at reviewing our current knowledge of the major synaptic molecular mechanisms alerted in neuropaediatric disorders.

**Rafael Artuch**, Clinical Biochemist, Chair of the Department of Inborn Errors of Metabolism of th Clinical Biochemistry Laboratory, and Group leader of the Unit-703 from CIBERER at the Inborn Errors of Metabolism Unit, **Hospital Sant Joan de Déu**, Barcelona, Spain

(See his CV at the Scientific Committee Section)

Coordinator of the SESSION 2: SYNAPTIC DETERMINANTS OF NEUROPAEDIATRIC DISORDERS II: FOCUSED ON GROUPS OF DISEASES

**José Maria Serratosa**, Chief of the Neurology Service and Director of the Eplilepsy Unit at the **Fundación Jiménez Díaz University Hospital**, and Associate Professor at the School of Medicine of the **Autonomous University of Madrid**, Madrid, Spain

José M Serratosa completed his undergraduate training and his postgraduate training in neurology at the Autonoma University of Madrid. He specialized in epilepsy with the support of fellowships from the Epilepsy Foundation of America at the California Comprehensive Epilepsy Program of the University of California Los Angeles where he then worked as an assistant research neurologist. Since 1995 he has been in charge of the Epilepsy Unit at the Fundación Jiménez Díaz Hospital in Madrid, Spain. His main research interests include the clinical and molecular genetics of the epilepsies, the functional study of epilepsy gene products, and the influence of genetic variations in the expression of particular common epilepsy phenotypes. He heads a research lab funded with public funds and his group forms part of the Centre for Biomedical Network Research on Rare Diseases (CIBERER). He has published numerous papers and book chapters in the field of epilepsy, mainly on the genetics of the epilepsies. He is a member of the editorial board of the journal Seizure and has been a member of the editorial board of Epileptic disorders, Epilepsy Research and has served as Associate Editor of Epilepsia. He has also served as a member of the Genetics Commission of the International League Against Epilepsy (ILAE). He is now the President of the Spanish Epilepsy Society.

**Synaptic Determinants of Epilepsy in Children**

**Nils Brose**, Director, Department of Molecular Neurobiology, **Max Planck Institute of Experimental Medicine**, Goettingen, Germany

Dr. Brose studied Biochemistry, Biology, and Physiology at the Universities of Tuebingen (Germany) and Oxford (UK). He received an MSc degree from the University of Oxford (UK), where he worked with Marianne Fillenz, and a PhD degree from the University of Munich (Germany), where he worked in the laboratory of Reinhard Jahn at the Max Planck Institute of Psychiatry. After postdoctoral training with Steve Heinemann (Salk Institute, La Jolla, CA, USA) and Tom Sudhof (UT Southwestern Medical Center, Dallas, TX, USA), Dr. Brose started his independent research program at the Max Planck Institute of Experimental Medicine (Goettingen. Germany), where he is currently the director of the Department of Molecular Neurobiology. Dr. Brose's research focuses on the molecular mechanisms of synaptogenesis and synapse function, and on the role of these processes in neuropsychiatric disorders.

**Neuroligins at Inhibitory Synapses - from Synaptogenesis to Autism Spectrum Disorders**

Members of the Neuroligin family of cell adhesion proteins are thought to regulate the generation, maturation, maintenance, and plasticity of synapses between nerve cells. Among the Neuroligin family members, the Neuroligin-2 and Neuroligin-4 isoforms are preferentially localised to inhibitory synapses, and loss-of-function mutations in Neuroligin-4 cause monogenic heritable forms of autism spectrum disorders (ASDs) in humans and ASD-like behavioral defects in mice. I will present biochemical, structural biology, cell biological, and electrophysiological data demonstrating that Neuroligin-2 and Neuroligin-4 regulate the recruitment of GABAA-receptors to nascent inhibitory synapses by activating the signaling/scaffold protein Collybistin. The main functional defects resulting from Neuroligin-4 loss in mice are subtle reductions in GABAA-receptor signaling in several brain regions, such as the CA3 region of the hippocampus, which lead to promient changes in oscillatory network activity. These data indicate that defects in GABAergic signaling and the consequent changes in network activity are causally involved in the ASD-like behavioral defects seen upon Neuroligin-4 mutation. Indeed, GABAergic dysfunction may be a common denominator of ASDs, because perturbed GABAergic signaling has been observed in several other ASD models.

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**Manju Kurian**, Paediatric Neurologist, Department of Neurology, Movement Disorders Unit, **Great Ormond Street Hospital**, London, UK

(See her CV at the Scientific Committee Section)

**Synaptic Determinants of Movement Disorders in Children**

Childhood movement disorders comprise a heterogenous group of conditions, including both hyperkinetic and hypokinetic phenotypes. A number of mechanisms underpin the pathophysiological basis of movement disorders, and include a number of proteins at the synaptic interface of networks within the basal ganglia and its connections to the thalamus, cortex and cerebellum. Determining the genetic basis of childhood movement disorders provides great insight into important mechanisms involved in motor control. In this talk, I will focus on childhood movement disorders and discuss how elucidating the genetic basis allows us to understand synaptic receptors, membrane channels/transporters and proteins involved in vesicle formation and recycling.

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**Àngels García-Cazorla**, Pediatric Neurologist. Coordinator of the Neurometabolic Unit and Principal Investigator of the Synaptic Metabolism Laboratory, **Hospital Sant Joan de Déu**, Barcelona, Spain

(See her CV at the Scientific Committee Section)

Coordinator of the SESSION 3: SYNAPTIC DETERMINANTS OF NEUROPAEDIATRIC DISORDERS III: FOCUSED ON MAIN GROUP OF MOLECULES INVOLVED IN SYNAPTIC COMMUNICATION

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**Carles Sindreu**, Principal Investigator, **University of Barcelona School of Medicine**, Barcelona, Spain

Carles Sindreu graduated in Biology at the University of Barcelona (UB), where he also obtained his PhD in Neurobiology. He undertook a postdoctoral stay at the University of Washington (UW), Seattle, working on molecular mechanisms of long-term memory . Carles Sindreu is currently a Ramon y Cajal investigator in the Pharmacology Unit, Universitat de Barcelona. Funded with competitive grants from the Spanish government and European Commission, his lab investigates signal transduction cascades and the neuronal circuits underlying episodic memory formation and retrieval. He is member of a nation-wide research network for the study of synapses in cognitive disabilities. He coordinates a multi-center research group on synaptic signaling supported by the Generalitat de Catalunya. He is also a member of several Neuroscience societies.

Coordinator of the SESSION 3: SYNAPTIC DETERMINANTS OF NEUROPAEDIATRIC DISORDERS III: FOCUSED ON MAIN GROUP OF MOLECULES INVOLVED IN SYNAPTIC COMMUNICATION

**Roser Pons**, Pediatric neurologist Assistant professor, Children's Hospital Agia Sofia, First Department of Pediatrics, **National and Kapodistrian University of Athens**, Athens, Greece

(See his CV at the Scientific Committee Section)

**Neurotransmitter Systems I. Disorders of Monoamines (Dopamine and Serotonin)**

The monoamines are neurotransmitters with multiple roles including psychomotor function, hormone secretion, cardiovascular, respiratory and gastrointestinal control, sleep mechanisms, body temperature and pain. Given the multiple functions of monoamines, disorders of their metabolism comprise a wide spectrum of manifestations, with motor dysfunction being the most prominent clinical feature. Analysis of their metabolites and pterins in spinal fluid assists in the diagnosis of these disorders. Treatment is based on medications that potentiate monoamine transmission. In this presentation, the different types of disorders of monoamines that have been described up till now will be discussed.

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**Elisenda Cortès**, Pediatrician, MD. Fellowship in Pediatric Neurology and Neurosciences in **Hospital Sant Joan de Déu**, Barcelona, Spain

Elisenda Cortès was Medical Doctor in 2006 by the Hospital Clínic, Barcelona, UB (University of Barcelona, Catalonia). 2007-2011. Degree in Pediatrics, Hospital Universitari Germans Trias i Pujol, UAB (Universitat Autònoma de Barcelona, Catalonia). 2011. Short fellowship in Neuropediatrics' Department in Tübingen Krankenhaus, Germany. 2010-2011. Course in Rare Metabolic Disorders (Curso de Formación en Enfermedades Raras Metabólicas), SEEIM (Sociedad Española de Errores Innatos del Metabolismo), Spain. 2012. Master in Neuroscience (Universidad Pablo de Olavide, Spain). Since 2012. Doctorand in Genetic and Neuroscience's Departments, main research on Rett syndrome and neurometabolic disorders, Hospital Sant Joan de Déu, University of Barcelona.

**Neurotransmitter Systems II. Disorders of GABA and Glutamate**

GABA is the main inhibitory neurotransmitter (NT) of the brain, while glutamate has an important role in brain excitability. Thus, maining a proper balance between these two NT is of crucial importance for brain development. GABA has also a prominent role in brain development, acting not only as a brain NT, but also as an important molecule for the metabolic and maturing status of the brain. Different disorders have been described so far related with these two NT. In this talk, we will focus on the clinical manifestations of: 1) disorders related with the synthesis and metabolism of these NT themselves (SSADH deficiency, mutations in GABA or glutamine receptors, etc), 2) disorders related with an imbalance in the excitatory/inhibitory status (Rett syndrome, fragile-X, etc), and 3) autoimmune disorders related with GABA or glutamate (anti-NMDA-R, GABA-A, etc)

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**Xavier Altafaj**, Team Leader, "Neurobiology of Ionotropic Glutamate Receptors in Health and Disease" Group, **Bellvitge Biomedical Research Institute** (IDIBELL), Barcelona, Spain

Principal Investigator ("Miguel Servet" programme, ISCIII) at the Neuropathology Department, Bellvitge Biomedical Reseacrh Institute (IDIBELL). After obtaining his degree in Molecular Biology by the University of Barcelona and the Université Libre de Bruxelles in 1997, he joined the Centre of Medical and Molecular Genetics (headed by Dr. Estivill) where he developed a Functional Genomics approach to understand the contribution of a candidate gene in the etiopathology of Down syndrome. In 2002 he obtained his PhD in Genetics and moved to the "Calcium channels: Functions and Pathology" (CEA, France, headed by Dr. De Waard), where he studied the crosstalk between the plasma membrane DHPR and the ER-spanning Ryanodine receptor (RyR). In 2007 he joined the laboratory of Dr. Fillat, at the Center for Genomic Research (CRG, Barcelona, Spain), where he developed gene therapy strategies for the potential rescue of cognitive alterations associated to Down syndrome, while he started to study the glutamate receptors in the brain of animal models of Down syndrome. His laboratory is currently focused to study the physiology of NMDA-type ionotropic glutamate receptors (iGluRs) and to unveil the molecular and cellular mechanisms bridging the gap between glutamate receptor dysfunctions and neurological diseases, towards the development of targeted therapeutic approaches. His efforts are focused to elucidate the molecular mechanisms underlying synaptic plasticity processes in post-synaptic glutamatergic neurons. The molecular insights are finally used to design targeted therapeutic approaches and to evaluate their efficacy to attenuate iGluR-mediated neuronal dysfunctions.

**Neurotransmitter Systems II. Disorders of GABA and Glutamate**

In his talk, Dr. Altafaj will present the current knowledge on Glutamatergic and GABAergic neurotransmitter systems in the developing brain. Briefly, he will show the physiological role of these neurotransmitter systems, that represent the main excitatory and inhibitory neurotransmission systems of the central nervous system. After this introduction, he will introduce the critical elements that regulate those systems, providing a broad view of the different molecular players acting not only in the neurotransmission communication (neurotransmitter release-neurotransmitter receptor), but also on those processes that regulate Glutamate and GABA metabolism (biosynthesis and catabolism), vesicle release, signaling pathways, recycling, etc,… The disturbance of these critical "checkpoints" may lead to neurotransmission-associated diseases, specially during the initial stages of life and brain development. These aspects, illustrated with experimental and clinical data, will be the starting point for further discussion on the challenging therapeutic opportunities, based on the targeting of the Glutamate and GABA neurotransmission systems.

**Sofia Duarte**, Neurologist, Clinical Researcher, Child Neurology Department, Hospital de Dona Estefânia, CHLC, **Instituto de Medicina Molecular**, Faculdade de Medicina da **Universidade de Lisboa**, Lisboa, Portugal

(See her CV at the Scientific Committee Section)

**Other Molecules involved in Synaptic Transmission and Disorders in Children**

The synapse is the functional unit for neuronal communication. Mutations in genes that encode relevant proteins for synaptic functions are being increasingly identified in neuropediatric disorders. After describing relevant roles of neuropeptides, neuromodulators, and neurotrophic factors, this talk will be focused on synaptic dysfunction in Rett Syndrome. This disease is mainly caused by mutations in the MECP2 gene and can be classified as a synaptopathy, since it comprises simultaneously impairments in synaptogenesis, synaptic maturation and synaptic plasticity. New insights about these dysfunctions will be discussed and also therapeutic strategies to overcome them.

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**Àngels García-Cazorla** Pediatric Neurologist. Coordinator of the Neurometabolic Unit and Principal Investigator of the Synaptic Metabolism Laboratory, **Hospital Sant Joan de Déu**, Barcelona, Spain

(See her CV at the Scientific Committee Section)

**Synaptic Metabolism: a New Approach to Study Neuropaediatric Disorders**

The synapse is a highly specialized structure with specific chemical composition and metabolic functions that are necessary for an appropriate neuronal communication and brain development. Neurometabolic diseases lead to abnormal concentration of metabolites in the brain. Most of them disturb important pre and post-synaptic functions leading to neurological symptoms such as intellectual disability, neuropsychiatric signs, epilepsy, and movement disorders. The description of "synaptic metabolic pathways" is an interesting approach to study mechanisms of disease and develop new therapeutic options in these disorders

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**Gabriella Horvath**, Biochemical Geneticist, **BC Children's Hospital** and **Vancouver General Hospital**, Vancouver, Canada

Gabriella Horvath, Biochemical Geneticist, BC Children's Hospital and Vancouver General Hospital, Vancouver, BC, Canada, since 2006. Main research interest is in primary and secondary neurotransmitter disorders and movement disorders in inborn errors of metabolism. Currently working on the research project: biogenic amine release from synaptic vesicle in presence of deficient intraneuronal calcium in sodium channel mutations. Another research area of interest is looking at phosphorylation status of biogenic amine synthetic enzymes in CSF in patients with secondary neurotransmitter deficiencies.

**Unraveling Secondary Neurotransmitter Deficiencies in Genetic Disorders**

Despite numerous reports of secondary CSF neurotransmitter deficiencies in genetic disorders, pathophysiology is still not fully understood. We reviwed 377 patients for whom CSF neurotransmitter analysis was performed between 2009-2013 in our centre. 70 had abnormal NT values; 2 identified with congenital NT disorders. The majority had primary epilepsy syndromes. 15 patients with secondary NT deficiencies and good. clinical response to L-dopa/carbidopa and 5-hydroxytryptophan in terms of improvement in seizures, psychiatric and/or movement disturbances were enrolled for whole exome Sequencing (Omics2TreatID study, Vancouver). Proteomic, metabolomic, protein phosphorylation studies, intracellular calcium content, full transcriptome analyses were conducted to validate genotypes and reveal mechanism of secondary NT deficiencies. Pathogenic mutations in genes encoding signal transductions pathways, chanellopathies, lysosomal protein, or splicing coactivator were identified. In 10 of 15 patients. In vitro experiments showed secondary NT deficiencies due to biogenic amine synthetic enzyme deficiency (inactive form of enzyme due to lack of phosphorylation), intracellular calcium signaling abnormalities, or up- and/or down-regulated genes in pathways related to biogenic amine metabolism. Using a systems biology approach, the complex pathophysiology of secondary neurotransmitter deficiencies was further elucidated. Therapy with dopamine and serotonin precursors is helpful in many cases.

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**Thomas Opladen**, Consultant for Child Neurology and Inborn Errors of Metabolism, Divsion of Child Neurology and Metabolic Medicine , **University Children Hospital Heidelberg**, Heidelberg, Germany

(See his CV at the Scientific Committee Section)

**The iNTD Registry: A New Clinical Database of Patients with Inborn Neurotransmitter, Pterin and Folate Disorders**

Inherited defects of neurotransmitter (biogenic amines), tetrahydrobiopterin (BH4) and folate metabolism lead to progressive neurological dysfunction in early infancy. Immediate diagnosis and treatment may result in an improved outcome. Until today there is no standardized systemic evaluation of diagnostic processes, therapeutic approaches and long term outcome of affected patients. The new "International Working Group on Neurotransmitter Related Disorders" (iNTD) provides a platform for the scientific and clinical exchange in the field of neurotransmitter related disorders. It includes 23 metabolic centers from 17 countries worldwide. The newly developed web-based iNTD patient registry for inherited defects of neurotransmitter, pterin and folate metabolism enables a standardized assessment of the epidemiology, genotype/phenotype correlation and outcome of these diseases, their impact on the quality of life of patients, and current diagnostic and therapeutic strategies. Based on the evaluation of the patient registry recommendations for the clinical and therapeutic management will be developed. The iNTD network is a growing international initiative to encourage scientific and clinical exchange on neurotransmitter related disorder. Together with the iNTD registry it aims to improve current research, basic knowledge and clinical management strategies considering the rare neurotransmitter related diseases.

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# INVITED SPEAKERS

## November, September, 27th, 2015

**Bru Cormand**, Associate Professor of Genetics, Department of Genetics, and Vice-Dean of Research, Faculty of Biology, **University of Barcelona**, Barcelona, Spain

Bru Cormand leads the Neurogenetics group at the Department of Genetics and he is a member of the Centre for Biomedical Network Research on Rare Diseases (CIBERER) and the Institute of Biomedicine of the University of Barcelona (IBUB). He works since 1992 on the genetic basis of mendelian and complex neurologic disorders, with stays in several research institutions (Medical Genetics Department, University of Helsinki; Vall d'Hebron Hospital, Barcelona; Genetics Unit, University Pompeu Fabra, Barcelona; Genetics Department, University of Barcelona). His research combines genetic, genomic and transcriptomic approaches in cells, animals and humans. He is a member of several international consortia, such as the Psychiatrics Genomics Consortium (PGC), the International Multicentre ADHD Genetics Consortium (IMAGE), the International Multicenter persistent ADHD Collaboration (IMpACT) and the International Headache Genetics Consortium (IHGC). Bru has coauthored more than 100 peer-reviewed papers in top journals like Nature Genetics, PNAS, American Journal of Human Genetics or Molecular Psychiatry.

Coordinator of the SESSION 4: BIOMARKERS, GENETICS, PROTEOMICS AND METABOLOMICS IN SYNAPTIC DISEASES

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**Xavier Altafaj**, Team Leader, "Neurobiology of Ionotropic Glutamate Receptors in Health and Disease" Group, **Bellvitge Biomedical Research Institute** (IDIBELL), Barcelona, Spain

(See his CV at the Session 3 Section)

Coordinator of the SESSION 4: BIOMARKERS, GENETICS, PROTEOMICS AND METABOLOMICS IN SYNAPTIC DISEASES

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**Benoit Colsch**, Life science division, Saclay Institute of Biology and Technology. Department of pharmacology and immunoanalysis. **CEA-Saclay**, Gif-sur-Yvette, France

He obtained his Ph. D in Bioorganic Chemistry (Univ. Pierre et Marie Curie, Paris 6, 2007). He joined a branch of National institute of Health (NIH/NIDA) at Baltimore (MD, USA) during 2 years (2008-2010) to develop lipidomics and Mass spectrometry imaging in Amina Woods's laboratory. He joined the Laboratory for Drug Metabolism Studies (CEA-LEMM) in 2011 to develop qualitative and quantitative methods using LC-MS in lipidomics in biological fluids and participate in metabolomics project in the field of neurosciences. He is also interested in biostastistical methods for the treatment of omics data.

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**Eduard Sabidó**, Head of the Proteomics Unit, **Centre de Regulació Genòmica** and **Universitat Pompeu Fabra**, Barcelona, Spain

Eduard Sabidó is the head of the CRG/UPF Proteomics Unit at the Centre for Genomic Regulation and University Pompeu Fabra. Eduard Sabidó holds a BS degree in Biochemistry (2003), Biology (2008) and Computer Science (2011), and a PhD in Biology (2009) from Universitat de Barcelona. He has made a postdoctoral stage at the Swiss Federal Institute of Technology (ETH Zürich, 2009-2012) and he did long- and short-term visits at the University of California in Davis and the Scripps Research Institute in San Diego. Dr. Eduard Sabidó has a broad experience in the fields of activity-based proteomics and targeted proteomics.

**Metabolomics and Proteomic of the CSF**

Mass spectrometry-based proteomics is an analytical technique for the identification and quantification of proteins and in the last few years it has emerged as a powerful analytical technique to discover protein biomarkers for neurological diseases. A particularly interesting application is the use of targeted proteomics assays to stratify patients and predict the prognosis of neural disease such as multiple sclerosis. In this talk we will illustrate how we took advantage of the capabilities of targeted mass spectrometry to establish a diagnostic molecular classifier with high sensitivity and specificity able to differentiate between clinically isolated syndrome patients with a high and a low risk of developing multiple sclerosis.

**Sakkubai Naidu**, Peditrician and Neurologist, **Kennedy Krieger Institute, Baltimore**, USA

(See her CV at the Session 1 Section)

**System Biology in Synaptic Disorders (Focused in Rett Syndrome)**

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**Judith Armstrong**, Facultative-Research scientist, **Hospital Sant Joan de Déu**, Barcelona, Spain

The research group in Rett syndrome has more than 20 years of experience. Dr. Armstrong is formed entirely in the field of Neurogenetics and hereditary neurological disease started in the studies of fragile X syndrome, work done during the past year in the Laboratory John F. Instituttet Kennedy, Denmark, under the direction of Dr. Grønskov and that meant obtaining a Masters degree in Human Genetics. She completed her doctoral training with Rett syndrome at Hospital Sant Joan de Deu de Barcelona, under the direction of Dr. Monros and the turning of the Tissue Bank for Neurological DNA of ICS Institute of Neuropathology (2003-2007), Hospital de Bellvitge under the direction of Dr. Ferrer and Dr. Volpini. Today and since 2008 she is Facultative-Research scientist in Section of Genetics and Molecular Medicine, Hospital Sant Joan de Deu de Barcelona and belongs to CIBERER U-703, responsible for research and molecular diagnosis of Rett Syndrome. Along with Dr. Pineda and since 2008, has resumed research projects in the RTT in the area of Molecular Genetics at the Hospital Sant Joan de Deu de Barcelona.The Rett Syndrome Group of the Hospital Sant Joan de Deu is a center of reference at national level, both clinical and molecular, logging more than 500 cases of RTT patients with clinical and genetic diagnosis confirmed

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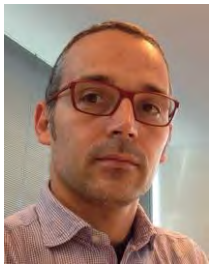

**Lluís Armengol**, CSO and CEO, **qGenomics,** Barcelona, Spain

Lluis Armengol, father of three and happily married. He received his PhD in biochemistry from the University of Barcelona in 2005. He carried out his thesis work between the disappeared IRO and the CRG institutes, actively working in the identification of genetics basis of complex diseases and genomic disorders. He mainly approached those challenges dealing with early genomic technologies and bioinformatics, that he continued to work with in his postdoc period at the CRG. Back in 2008, he moved to the dark side of science and co-founded qGenomics, together with Profs. Estivill and Pérez-Jurado. At qGenomics, we combine basic and applied research in the rare diseases field, with the translation of genomic knowledge into real and usable tools for diagnostic of human diseases. He continues linked to the academia by collaborating in different master degrees from different universities, as well as an associate editor for a couple international journals in the field of medical genomics. He is currently the CSO and CEO at qGenomics.

**Genetic Tools Focused on Diagnosis**

NGS technology has enabled to develop methodologies for the capture of all the genome coding regions (>20,300 coding gene in GRCh28), termed as whole-exome sequencing (WES). The success in WES comes by the exome-captured regions and its coverage. The weakest point in WES is that the capture of target sequences is not uniform across the genome. In consequence, a fraction of the coding regions could remain unsequenced. False-negative and false-positive rates are higher than in targeted panels, adding a layer of complexity and uncertainty to the diagnosis. Post NGS, powerful bioinformatics tools are used to assess all the high throughput data. The sequence analysis follows specific and versatile bioinformatics pipelines with quality control steps, read cleaning, assembly, annotation and SNP calling. Variant analysis is a constant game of filtering in and out depending on the specific traits of a pedigree. Generally, selecting an inheritance mode and ruling out common SNPs present in the databases, the list of candidate genes reduces drastically. Subsequent study and selection of candidates implicates the fusion of biological and clinical criteria. Whole-genome sequencing (WGS) overpasses these limitations of the WES, since the capture step is not necessary. However, its application in the clinical diagnosis is at present very limited. Nevertheless, these two approaches may be optimal for elucidation of molecular basis of new diseases. Targeted-capture NGS strategies may be of choice for a first step molecular studies of intellectual disability, autism spectrum disorder, neuropaediatric diseases in general and for Rett syndrome (RTT) in particular. Because the targeted region is smaller, gene panel strategies present an improvement in contrast to WES, as better sequence coverage can be achieved. For clinical diagnosis, this approach is highly valuable not only for detecting mutations, but also for being capable to rule out candidate genes as causative of the pathology, and consequently, a positive or negative diagnostic report for physicians and families may be done. Thus, the lack of false-negative results assures a major reliability, indispensable in the diagnostic field. Deeper coverage also favors the detection of copy number variants, which should also be ruled out in target genes, taking into account that NGS approaches do not display all kinds of genetic variation susceptible to cause a disease. Our experience in clinical and genetic diagnostic with RTT using targeted-NGS by panel of genes allow us to study a larger number of genes associated with RTT simultaneously, significantly reducing response time and the cost of the study. It also allows us to study other related clinical RTT and thus to redirect the clinical diagnosis to another disease genes: Angelman syndrome, Pitt-Hopkins syndrome, Dravet syndrome,....Verification by Sanger sequencing of the progenitors of the mutations detected by NGS remains essential for their characterization as well as perform functional studies.

**Vesna Prchkovska**, co-founder and CSO, **Mint Labs**, Barcelona, Spain

Vesna Prchkovska graduated with honours in Electrical Engineering at Ss. Cyril and Methodius University in Skopje (Macedonia) and obtained her PhD at the Eindhoven University of Technology (Netherlands). She based her doctoral degree in novel diffusion-based MRI imaging models. She later became a Marie Curie post-doctorate research fellow at IDIBAPS, Barcelona where she researched novel imaging markers for neurodegenerative diseases such as Multiple Sclerosis. In 2013, she was an invited researcher at Harvard Univeristy, Martinos Center at the Ageing Group. She has 3 years of experience in research with brain diseases and over 8 years expertise in medical image processing and visualization. She is a co-founder and CSO of Mint Labs, the first multimodal imaging platform that integrates and analyzes MRI images in order to quantify and measure changes in the brain for accelerating the drug development process in pharmaceutical clinical trials.

Coordinator of the SESSION 5: BRAIN NETWORKS AND CIRCUITRIES

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**J. Antoni Ramos-Quiroga**, Section Chief of Adult Psychiatry and Coordinator of the ADHD Program in the Department of Psychiatry at the **Hospital Universitari Vall d'Hebron**, Barcelona

Associate Professor of Psychiatry at the Universitat Autònoma de Barcelona, Spain, and Section Chief of Adult Psychiatry and Coordinator of the ADHD Program in the Department of Psychiatry at the Hospital Universitari Vall d'Hebron in Barcelona. His group is member of the Centre for Biomedical Network Research on Mental Health (CIBERSAM). He is the Chair of the Section "Neurodevelopmental Disorders Across the Lifespan" of the European Psychiatric Association. Prof. Ramos-Quiroga's research focuses on ADHD in adolescents and adults, including clinical trials, drug trials, neuroimaging studies and genetics. He is a member of the European Network Adult ADHD, the International Multi-centre persistent ADHD CollaboraTion (IMpACT), the International Collaboration on ADHD and Substance Abuse (ICASA) and Psychiatric Genomics Consortium (PGC). He is the author of more than 106 international publications and five books, and has presented at national and international conferences on ADHD. He has participated in several groups of government experts on ADHD. He is a speaker at national and international conferences on ADHD. He organizes Theoretical and Practical Courses "ADHD across the life" of the Hospital Universitari Vall d'Hebron (15th edition).

Coordinator of the SESSION 5: BRAIN NETWORKS AND CIRCUITRIES

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**Paulo Rodrigues**, CEO and co-founder of **Mint Labs**, Barcelona, Spain

Paulo graduated in Computer Science Engineering at the University of Minho (Portugal) and obtained a PhD at the Eindhoven University of Technology (Netherlands). His research focused on developing novel tools for the virtual dissection of the human brain white matter structures. He published several papers where image analysis techniques were explored to improve the analysis and visualization of diffusion weighted MRI. After the PhD work, he held a software engineering position, for 1 year, in a successful Dutch IT company, leader in advanced planning and scheduling solutions, based on an inspiring general solution. He held a research associate position at the Department of Personality, Faculty of Psychology, Universitat Barcelona, Spain, where he exploited neuroimaging techniques, especially diffusion imaging, to explore the neurobiological mechanisms in cognitive functions and disorders. Since 2013, he is the CEO and co-founder of Mint Labs, a award winning cloud based platform for the processing and management of neuroimaging data, and has been awarded the MIT Technology Review Innovative Entrepreneur under 35.

**Connectomics in Neuropaediatric Disorders**

The study of the brain connectivity and the connectome has opened new experimental and theoretical avenues in many areas of neuroscience such as neuroanatomy, functional brain imaging or neurodevelopment. Pathological perturbations of the brain are rarely confined to a single locus; instead, they often spread via axonal pathways to influence other regions. Patterns of such disease propagation are constrained by the extraordinarily complex, yet highly organized, topology of the underlying neural architecture; the so-called connectome. For instance, patients affected by Rett Syndrome experience numerous symptoms, across multiple circuits, including movement and language problems, autism-like features, and often epilepsy. Here, we consider how network views of the brain can help understand these complex pathologies. The talk we give an overview on the connectomics methodologies and introduce new applications in neuropaediatrics.

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**J. Antoni Ramos-Quiroga**, Section Chief of Adult Psychiatry and Coordinator of the ADHD Program in the Department of Psychiatry at the **Hospital Universitari Vall d'Hebron**, Barcelona

(See his CV at the Session 5 Section)

**Brain Development in Neuropsychiatric Disorders: ADHD**

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder. ADHD has been associated with various structural and functional brain abnormalities. Cross-sectional

anatomical imaging studies of ADHD consistently point to involvement of the frontal lobes, parietal lobes, basal ganglia, corpus callosum, and cerebellum. Because in more than 50% of the children ADHD can persist into adulthood, longitudinal studies have been of particular interest. Such studies indicate a developmental delay of cortical thickness trajectories mainly for the frontal lobes. The talk will review the state of art about brain neurodevelopment and ADHD.

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**Xavier Castellanos**, Brooke and Daniel Neidich Professor of Child and Adolescent Psychiatry; Professor of Radiology; Director of Research; Director of the Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, **New York University School of Medicine**, New York, USA

F. Xavier Castellanos, MD, a renowned neuroscientist, has devoted his career to developing innovative research techniques to deepen our understanding of both healthy and pathological brain processes. Dr. Castellanos is the vice-chair of research in the NYU Child Study Center, director of Center's Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, Brooke and Daniel Neidich Professor of Child and Adolescent Psychiatry and professor of radiology and physiology and neuroscience at the NYU School of Medicine. Prior to joining the NYU faculty, Dr. Castellanos worked for 10 years as a staff physician and chief of the ADHD Research Unit at the National Institute of Mental Health (NIMH). As co-chair of the American Psychiatric Association Workgroup on ADHD and Disruptive Behavior Disorders, he is a key contributor to the forthcoming fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). His research has been widely published in peer-reviewed journals, including the Journal of the American Medical Association, The American Journal of Psychiatry, Archives of General Psychiatry, Biological Psychiatry, Nature Neuroscience, Nature Reviews Neuroscience, and Trends in Cognitive Sciences.

**Brain Networks in Neuropsychiatric Disorders in Children**

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**Soledad Alcántara**, Associate Professor, Department of Pathology and Experimental Therapeutics, School of Medicine (Bellvitge Campus) **University of Barcelona**, Barcelona, Spain

(See her CV at the Scientific Committee Section)

Coordinator of the SESSION 6: MODELS AND NEW THERAPEUTIC APPROACHES FOR SYNAPTIC DISEASES

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**Pau Gorostiza**, ICREA Research Professor at the Institute for Bioengineering of Catalonia (**IBEC**), Barcelona, Spain

Pau Gorostiza graduated in physics at the Universitat de Barcelona (UB), where he also obtained his Ph.D. (European Doctorate) in the field of semiconductor electrochemistry. He also worked at the microscopy facility of the UB, where he gained experience in AFM and STM of biological samples, as well as in nanotechnology applied to materials science. He has visited the CNRS and the Université Pierre et Marie Curie in Paris (France), and the University of California at Berkeley (USA). His recent works include the development of optical switches for remotely controlling neuronal activity. He obtained a Young Biomedical Investigator Award of the Francisco Cobos Foundation, a Career Development Award of the Human Frontier Science Program (HFSP) and Starting and Proof-of-Concept grants of the European Research Council (ERC). He is currently ICREA Research Professor at the Institute for Bioengineering of Catalonia (IBEC).

Coordinator of the SESSION 6: MODELS AND NEW THERAPEUTIC APPROACHES FOR SYNAPTIC DISEASES

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**Héctor Díez**, Postdoctoral researcher in Synaptic Metabolism Laboratory", **Fundación Sant Joan de Déu**, Barcelona, Spain

Researcher in neurobiology. He got his PhD in Molecullar Biology and Biochemistry for Universidad Autónoma de Madrid in 2010 for a work studying molecular basis of development and survival of cultured neurons. He has been involved in research of protein biochemistry and culture models of the nervous system for more than ten years in laboratories of Instituto Cajal (CSIC), CBMSO (CSIC/UAM) or CIBERNed. He currently works in Àngels Garcia-Cazorla's group in Fundación Sant Joan de Déu, developing models for the study of rare diseases of the nervous system, mainly Tyrosine Hydroxylase Deficiency, Rett Syndrome and extremely rare cases of infantile lethal parkinsonism.

### Current Cellular Models of Synaptic Diseases

Cell cultures are a powerful in vitro tool for preclinical studies of neuropaediatric diseases. Since the classical primary cultures and immortalized cell lines to the growing field of induced pluripotent stem cells, cultured cells have been employed for decades in medical research. In this talk, we will present a (necessarily) brief review of the different kind of cultures and their applicability in the study of neuropaediatric disorders..

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**Soledad Alcántara**, Associate Professor, Department of Pathology and Experimental Therapeutics, School of Medicine (Bellvitge Campus) **University of Barcelona**, Barcelona, Spain

(See his CV at the Scientific Committee Section)

### Animal Models of Synaptic Diseases

The lecture will start from the notion that animal models are imperfect copies of human diseases, reviewing our current knowledge of synaptic development and pathology, and animal models. The relevant considerations when modeling a disease of synaptic development with the aim of increasing the success of translational research will be discussed.

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**Mara Dierssen**, Group Leader at **Centre for Genomic Regulation** (CRG) and Institut Municipal d'Investigacions Mèdiques (IMIM), Barcelona, Spain

Dr. Dierssen research builds on multi-level exploration of neural networks and dynamical models to get insight in the integrative principles in brain cognitive systems, mainly using genetically modified mouse models of intellectual disability and other cognition disorders. The overall goal of her research is understanding how putative candidate genes for human complex genetic diseases impair the neuronal connectivity with consequences on brain cognitive systems. She is a world expert in the field of intellectual and has received several recognitions for her work (Ramón Trias Fargas, Jaime Blanco or Sisley-Lejeune Awards). Dr Dierssen is the President of the Spanish Society of Neuroscience, past president of the International Behavioral and Neural Genetics Society, and member of the Executive Committee of the Federation of European Neurosciences Societies, EDAB and Academia Europaea. She was associated professor of the University of Cantabria and the University Ramon Llull in Barcelona, and has organized a large number of courses and conferences. She is part of several Editorial Boards (Acta Neuropathologica, Genes Brain and Behavior, Frontiers in Behavioral Neuroscience, Down Syndrome Research and Practice, Amino Acids, Frontiers in Genetics and BMC).

### Pharmacological Approaches for Synaptic Disorders

Recent insights into the neurobiological mechanisms of intellectual disability (ID) have shown that despite the broad spectrum of genetic and environmental aetiologies, alterations in neural plasticity are common neuropathological findings. Numerous ID genes converge on overlapping molecular networks thus opening the possibility to discover drugs for restoring cognitive function not restricted to a specific ID disorder. Over time, abnormal neural plasticity leads to a cognitive impairment regardless of the particular molecular cause. Thus, drugs targeting core molecules in neural plasticity cascades could set the brain in a favourable state for cognitive function and be disease-modifying treatments in individuals with ID of different genetic and environmental aetiologies. However, in addition to pharmacological interventions, it is necessary to explore novel non-pharmacological therapeutic avenues that can potentially play a key role as safe and effective co-adjuvants for further enhancing the positive effects of experimental compounds.

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**Aurora Martínez**, Professor, Department of Biochemistry, **University of Bergen**, Norway

(See her CV at the Scientific Committee Section)

### Chaperone Therapy for Synaptic Disorders

Tyrosine hydroxylase (TH) is a (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4)-dependent enzyme that catalyzes the rate-limiting enzyme in the synthesis of catecholamine neurotransmitters (dopamine, noradrenaline, adrenaline). Variants in the TH gene are responsible for the rare autosomal recessive disorder TH deficiency (THD) associated with defective catecholamine synthesis. The diagnosis of THD is based on clinical symptoms and measurement of the catecholamine metabolites HVA and MHPG in cerebrospinal fluid, which are present in lower concentrations in THD patients. THD phenotypes span from L-DOPA-responsive dystonia, with infantile onset (type A) or a more severe L-DOPA-non-responsive encephalopathy, with neonatal onset (type B), and suspected synaptic disorder. Most of the 40 reported mutations in THD appear to critically misfold TH and reduce the stability of the enzyme in vitro. The degree of misfolding correlates well with the severity of the patient phenotypes, underlying the relevance of searching for stabilizing compounds that correct misfolding and may protect from loss of protein and activity in vivo (pharmacological chaperones). A recent study with TH has revealed different mechanisms for the action of pharmacological chaperones and identifies a subtype of compounds that preserve TH activity by weak binding to the catalytic iron (Hole et al. (2015); BBA 1854: 1078-89). The stabilizing effect of these compounds has been established in vitro and in cells. A recent mice model of THD type B (Korner et al. (2015) Brain 138: 2948-63) represents an optimal frame for testing synergistic combinations of different pharmacological chaperones that could provide patient-tailored therapeutic options for THD.

**Cristina Fillat**, Group Leader of the Gene Therapy and Cancer Group, **Institut d'Investigacions Biomèdiques August Pi i Sunyer** (IDIBAPS), Barcelona, Spain

She studied Pharmacy at the University of Barcelona and obtained a PhD in Biochemistry at the Autonomous University of Barcelona. She initiated in the field of Gene Therapy during her postdoctoral stage at Mount Sinai School of Medicine in New York, working on lysosomal storage diseases. Later she was appointed investigator at the Centre for Medical and Molecular Genetics-IRO, Barcelona, conducting several research projects on Down syndrome and cancer with the dual goal of acquiring a broad understanding of the molecular and pathophysiological basis of the diseases and to conduct preclinical gene therapy development. In the period 2002-2011 she joined the Centre for Genomic Regulation as a Group Leader and in 2007 became PI at the Centre for Biomedical Network Research on Rare Diseases (CIBERER). Since 2011 she leads a research group in Gene Therapy and Cancer at IDIBAPS, Barcelona (consolidated group 2014SGR-248). Over the years she has contributed to the gene therapy field with more than 80 publications. She was among the team members that promote the constitution of the Spanish Society of Gene and Cell Therapy and served as Scientific Secretary from 2005 to 2011. She is editorial board member of several journals, highlighting Molecular Theray-Oncolytics and Current Gene Therapy.

### Gene Therapy in Synaptic Disorders

Therapeutic challenge of neurological diseases involving synaptic pathology explore several gene therapy strategies aimed to remodel synaptic structure and induce neurosynaptic plasticity to improve function. In this presentation we will discuss on the more current approaches that are being tested and the most common gene delivery vectors. Relevant examples of gene therapy studies, as well as outstanding challenges will be discussed.

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**Pau Gorostiza**, ICREA Research Professor at the Institute for Bioengineering of Catalonia (**IBEC**), Barcelona, Spain

(See his CV at the Session 6 Section)

### Manipulation of Biological Activity with Light

The manipulation of biological processes with light using optogenetics has revolutionized experimental neurobiology. Optogenetic manipulation of neuronal activity is based on the expression of light-sensitive proteins, which often alters cellular physiology and also limits its therapeutic applications due to the need of gene therapy in the case of human subjects. A powerful complement and alternative to optogenetics is offered by optopharmacology (the development of light-regulated drugs like receptor agonists, antagonists and modulators), which has the advantage that it can operate on endogenous receptors without genetic manipulation. Unlike optogenetics, optopharmacology involves small molecules that (1) can be validated and approved using standard "drug development" procedures, and (2) constitute a single component that can be applied directly to wildtype organisms, including humans. Despite the advances in the development of pharmacologically specific drugs for a large fraction of therapeutic target proteins in humans, important challenges remain unsolved, including the control of the drug action site, the time course of drug effect, and the fine-tuning of drug effects on target tissue. In this proposal, we aim to address these issues by using drugs with light-dependent properties (i.e. affinity and/or efficacy) in order to regulate the activity of endogenous proteins. The administration of a photocontrolled drug in combination with illumination that is patterned in space and time would provide a novel degree of control and regulation of drug action. This method would allow precisely focusing on a target tissue and controlling drug doses with time, thus reducing side effects due to target receptors located in non-targeted tissues. We have recently developed several novel optopharmacological tools, including light-regulated peptide inhibitors of protein-protein interactions and light-regulated orthosteric and allosteric modulators of glutamate receptors. Their design, characterization and possible applications will be discussed.

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# PRACTICAL INFORMATION

## Venue


CosmoCaixa Barcelona
Àgora Room
C/ Isaac Newton, 26  08022 Barcelona, Spain
obrasocial.lacaixa.es/laCaixaFoundation/home_en.html

## Contact person during the event

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# ADDITIONAL INFORMATION

## Suggested Reading

### SYNAPTIC DETERMINANTS OF DISEASES

**Major synaptic signaling pathways involved in intellectual disability**
Pavlowsky A et al. Mol Psychiatry. 2012
Genetic causes of intellectual disability (ID) include mutations in proteins with various functions. However, many of these proteins are enriched in synapses and recent investigations point out their crucial role in the subtle regulation of synaptic activity and dendritic spine morphogenesis. Moreover, in addition to genetic data, functional and animal model studies are providing compelling evidence that supports the emerging unifying synapse-based theory for cognitive deficit.

**Neurotransmission and synaptic function in epilepsy: Pathway-driven discovery of epilepsy genes**
Noebels J. Nat Neurosci. 2015 Mar;18(3):344-50.
This review explains how in epileptic disorders every facet of neurotransmission, from dendritic spine to exocytotic machinery, is in play, and defects of synaptic inhibition are over-represented. Because seizures stand at the crossroads of all neuronal synchronization disorders in the developing and aging brain, the neurobiological analysis of epilepsy-associated genes provides an extraordinary gateway to new insights into higher cortical function.

**Monoamine neurotransmitter disorders-clinical advances and future perspectives**
Ng J, et al. Nat Rev Neurol. 2015
The monoamine neurotransmitter disorders are important genetic syndromes that cause disturbances in catecholamine (dopamine, noradrenaline and adrenaline) and serotonin homeostasis. These disorders result in aberrant monoamine synthesis, metabolism and transport. The clinical phenotypes are predominantly neurological, and symptoms resemble other childhood neurological disorders, such as dystonic or dyskinetic cerebral palsy, hypoxic ischaemic encephalopathy and movement disorders. Therapeutic intervention can lead to complete resolution of motor symptoms in some conditions, and considerably improve quality of life in others.

### NEW TOOLS IN DIAGNOSIS AND DETECTION OF BIOMARKERS

**Lipidomic analysis of cerebrospinal fluid by mass spectrometry-based methods**
Colsch B, et al. J Inherit Metab Dis. 2015

**Mass spectrometry-based proteomics for systems biology**
Sabidó E et al,Curr Opin Biotechnol. 2012

### BRAIN NETWORKS

**The Human Connectome Project**
Mapping of the human connectome offers a unique opportunity to understand the complete details of neural connectivity (Sporns et al., 2005, Wedeen et al., 2008, Hagmann et al., 2007). The Human Connectome Project (HCP) is a project to construct a map of the complete structural and functional neural connections in vivo within and across individuals. The HCP represents the first large-scale attempt to collect and share data of a scope and detail sufficient to begin the process of addressing deeply fundamental questions about human connectional anatomy and variation.
http://www.humanconnectomeproject.org/

**Reproducibility of the Structural Connectome Reconstruction across Diffusion Methods**
Prčkovska V, et al J Neuroimaging. 2015

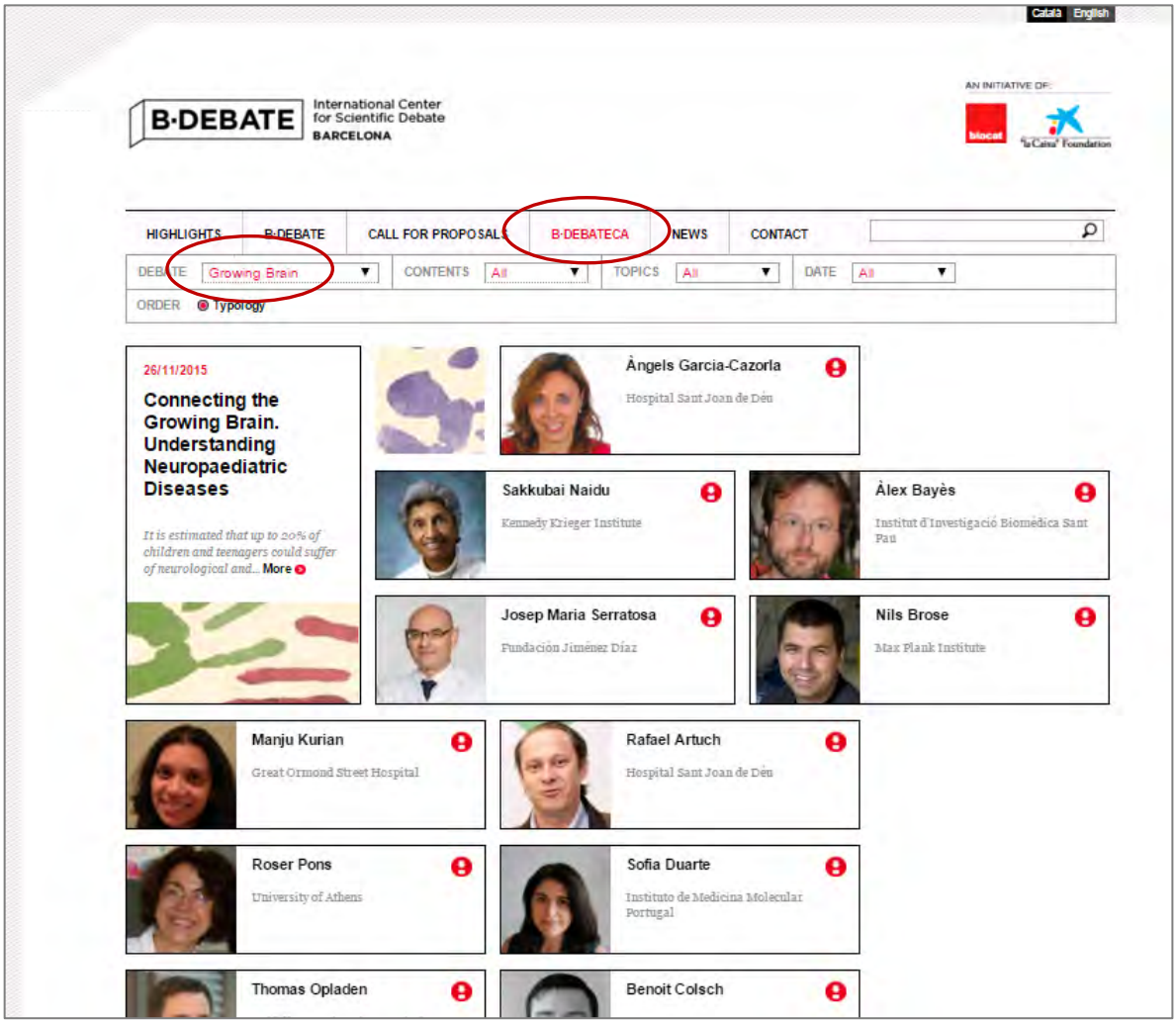
**White matter microstructure and the variable adult outcome in chidlhood ADHD**
Shaw et al. Neuropsychopharmacology 2015

# OUTCOMES

## B·Debateca

On the website of **B·Debate**, you will find all the information related with the celebration of the meeting that includes reports, conclusions, scientific documents, interviews with the experts, speaker's CVs, videos, images, press documentation and other related materials. We invite you to visit the section **B·Debateca** on www.bdebate.org

Contents of the meeting "CONNECTING THE GROWING BRAIN. UNDERSTANDING NEUROPAEDIATRIC DISEASES THROUGH SYNAPTIC COMMUNICATION"

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**#GrowingBrain**

# ORGANIZERS


**B·Debate** International Center for Scientific Debate Barcelona is a **Biocat** initiative with support from **"la Caixa" Foundation**. It drives first-rate international scientific debates, to foster dialogue, collaboration and open exchange of knowledge with prestigious national and international experts, to approach complex challenges of high social interest in life sciences. B·Debate sees debate as a powerful, effective way to generate knowledge and strives to help position Barcelona as a benchmark in generating knowledge a nd Catalonia as a country of scientific excellence.

B·Debate sees debate as a powerful, effective way to generate new knowledge. The debates are top-notch international scientific meetings featuring a selection of experts of renowned international prestige and scientists that work in Barcelona and Catalonia, moderated by scientific leaders. Since 2009 B·Debate has invited about 1200 recognized speakers and over 7.000 attendees. B·Debate seeks out answers to the challenges and needs of society in the field of life sciences, taking into account the complex, ever-changing conditions of this global world. The debates foster the integration of different disciplines of science and deal with such diverse topics as ageing, new therapeutic approaches to various diseases, innovative technology to improve knowledge of the human genome, food resources, new tools to integrate knowledge management, clinical genomics, neurosciences, climate change, and new energy sources, among others. The knowledge and results obtained through these events is spread throughout both the scientific community and general society through the various **B·Debate** channels and instruments.

More info: www.bdebate.org


**Hospital Sant Joan de Déu** is a teaching hospital specializing in the fields of pediatrics, gynecology and obstetrics. It is located in Barcelona, Catalonia (Spain). It is a privately owned center, concerted by the Catalan Public Health Service, which belongs to the Hospitaller Order of St. John of God, religious organization that manages more than 300 health centers over the world. The center has 362 beds and 12 opearting rooms. It emplys more than 1.500 professionals and attends every year more than 3.000 births, 130.000 emergencies, records 26.000 hospitalizations and 13.000 surgeries are performed. Hospital Sant Joan de Déu is the largest children's hosptial in Spain, and one of the top 5 in Europe, along with Great Ormond Street (London), Hospital Necker Enfants Malades (Paris) and Ospedale Meyer (Florence).

More info: www.hsjdbcn.org


**Fundació Sant Joan de Déu** (FSJD) is a private, non for profit institution located in Barcelona, Spain. FSJD promotes and develops innovative biomedical research with the aim of contributing to the improvement of people's health and wellbeing. Research and innovation activities at FSJD covers 7 areas of expertise, primarily in the fields of maternal and child health and mental heath, but also addresses other socially disadvantaged groups.

More info: www.fsjd.org/es

# COLLABORATORS

**CosmoCaixa** offers interactive, enjoyable science and an open door for anyone who is eager to learn and understand and who never stops wondering why things are the way they are. **CosmoCaixa Barcelona** boasts the Geological Wall and the Amazon Flooded Forest, which features more than 100 plant and animal species that convince visitors they have been transported from the Mediterranean to the very heart of the tropical jungle. In addition to its permanent facilities and its open areas, CosmoCaixa offers a scientific and educational programme that includes exhibitions, workshops, conferences, courses and debates involving experts from all over the world.

More info: obrasocial.lacaixa.es

**Eisai's** corporate concept is to give first thought to patients and families, and to increase the benefits that healthcare provides. Under this concept, Eisai endeavours to become a human health care (hhc) company.
Eisai's mission is the enhancement of patient satisfaction. Eisai believes that revenues and earnings will be generated as a consequence of fulfilment of the mission. Eisai places importance on this positive sequence of the mission and the ensuing results.
Positioning Compliance, the observance of legal and ethical standards, as a core in all business activities, Eisai strives to fulfil corporate social responsibilities.

More info:www.eisai.com

**Connecting The Growing Brain** is a network of specialised clinicians and researchers who aim to understand the developing brain through synaptic communication. We develop an interacting work based on multi-level integration studies of the synapse (metabolic, proteomic, brain image, connectome studies, cellular and animal models) in neurometabolic and neurogenetic disorders. We have initially focused in inherited disorders of neurotransmitters and Rett syndrome. Additionally, www.connectingthegrowingbrain.com is an information portal about neurotransmitters, cellular neurochemistry and synaptic communication in neuropaediatric diseases and belongs to the international project for the study of neurotransmitter disorders iNTD.

More info: www.connectingthegrowingbrain.com


The **I-NTD: International Working Group On Neurotransmitter Related Disorders i**s an international network that includes different centers from Europe, the United States and Asia. The major goal of the project is to set-up a web-based patient registry for inherited defects of neurotransmitter, pterin and folate metabolism. This aims to provide a basis for improving our understanding of the epidemiology, genotype/phenotype correlation and outcome of these diseases, their impact on the quality of life of patients, and for evaluating diagnostic and therapeutic strategies.

More info: www.intd-online.org

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# NOTES

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VENUE:

**CosmoCaixa Barcelona**
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