ERA-NET NEURON

NEWSLETTER 38

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Announcements from NEURON

DON'T MISS

2022 Call for Proposals on "Cerebrovascular Diseases"

Pre-proposal submission deadline:
8 March 2022, 14:00 CET
Click for details

COMING UP!

Virtual Meeting on European Biomedical Research Infrastructures' Resources for Researchers in Neurosciences
February 1st & 3rd, 2022
Click for details

From the desk of the coordinator | January 2022


Marlies Dorlöchter

Dear All,

We at the ERA-Net NEURON continue working passionately to fund, support and encourage excellent, innovative and collaborative neuroscience research despite the fact that we end another year and begin a new one with the pandemic still very much affecting and constraining our lives and cooperation.

In this issue of the newsletter we present the 18 consortia that are funded under our Joint Transnational Call 2021 (JTC2021) on 'Neurodevelopmental Disorders'. The European Commission (EC) is joining the NEURON network in this particular call and contributing to the funding scheme, which allows us to fund more proposals than usual. Read more about the call, its outcomes and the funded projects on page 3.

For relevant and applicable brain research to be carried out, engaging of patients and caregivers as well as the public is necessary. The ERA-Net NEURON, therefore, seeks to strengthen public and patient involvement in biomedical research. We invited 11 international patient experts to review the full proposals of JTC 2021 on Neurodevelopmental Disorders from the perspective of patients and carers, as part of our board of scientific

Funded by the European Commission

More information can be found on our website
http://www.neuron-eranet.eu/index.php
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experts. Two of them wrote a commentary on how the collaboration of patients and researchers can improve the outcome of biomedical research. This commentary describes what proper patient involvement should entail, how it can be worked out at each step of a research project, and reflects on what has to be considered to do it in a meaningful way.

Furthermore, public engagement is essential for raising awareness to various neurological and mental disorders and illuminate the great importance of brain research and the investment in it. We therefore launched the ERA-Net NEURON lecture series for lay audience. The first lecture was an open webinar that took place on October 29th - "World Stroke Day" – on 'Challenges and opportunities in stroke care and research' by Prof. Dr. Martin Dichgans, Director of the Institute for Stroke and Dementia Research at the Medical Center of the University of Munich. Stay posted for future lectures.

Collaboration is key for us at NEURON, as stated in the slogan of our strategic meeting in January last year "Together for Brain Research". To portray this, I took part in roundtable discussions at the European Brain Summit in October, to talk about the need of collaboration in brain research at European and global levels. This kind of engagement with the EU commission and national policy makers about strategic questions is important for future developments, such as creation of a Brain Health Partnership to ensure the continued support for outstanding groundbreaking brain and neuroscience research in Europe.

Finally, please keep up with our website, follow us on twitter and join our LinkedIn group in order to join our community and not to miss further information about our various calls, activities and events.

Sincerely yours

NEURON Joint Transnational Call 2021: "Neurodevelopmental Disorders"

Neurodevelopmental disorders severely curtail the quality of life of patients and their families, often throughout their entire lifespan. Thus, research on neurodevelopmental disorders and its translation into diagnostic and therapeutic outcomes is a central pillar to promote healthy living in Europe and worldwide.

A board of internationally renowned scientists evaluted the proposals and eighteen multinational research consortia were selected for funding under JTC2021 on the topic of 'Neurodevelopmental Disorders', which is co-funded by the European Commission. In total, 80 research groups from 16 NEURON partner countries collaborate in these projects, which cover various neurodevelopmental disorders and numerous methodological approaches. The total funding volume of the call amounts to about 19.2 M€.

As part of ERA-Net NEURON's mission to actively involve patients in the biomedical research process, proposals of the Joint Transnational Call 2021 on Neurodevelopmental Disorders underwent a patient review as part of the evaluation process. Eleven international patient experts reviewed the full proposals from the perspective of patients and carers. Besides providing a full written evaluation to the applicants, the patients actively participated in the discussion at the review panel meeting to advocate for their appraisals and concerns. Two of this year's patient-reviewers joint forces to write a commentary on how the collaboration of patients and researchers can improve the outcome of biomedical research from their perspective. This commentary can now be found on the NEURON website.

We wish all the funded consortia great success and remarkable achievements and hope their outcomes may one day assist in the prevention, diagnosis, therapy and/or rehabilitation of people with neurodevelopmental disorders!

Sylvain Rheims

AUTONOMIC

Neurodevelopmental impact of epilepsy on autonomic function in Dravet Syndrome

Project Coordinator:

Sylvain Rheims, Dept. of Functional Neurology and Epileptology (Hospices Civils de Lyon and Lyon 1 University) and Lyon's Neuroscience Research Centre (INSERM U1028/CNRS UMR5292/Lyon 1 University) Lyon, France

Project Partners:

Rainer Surges, Dept. of Epileptology, University Hospital Bonn, Bonn, Germany

Stijn Verhulst, Dept. of Paediatrics and Paediatric Neurology, Antwerp University Hospital, Antwerp, Belgium

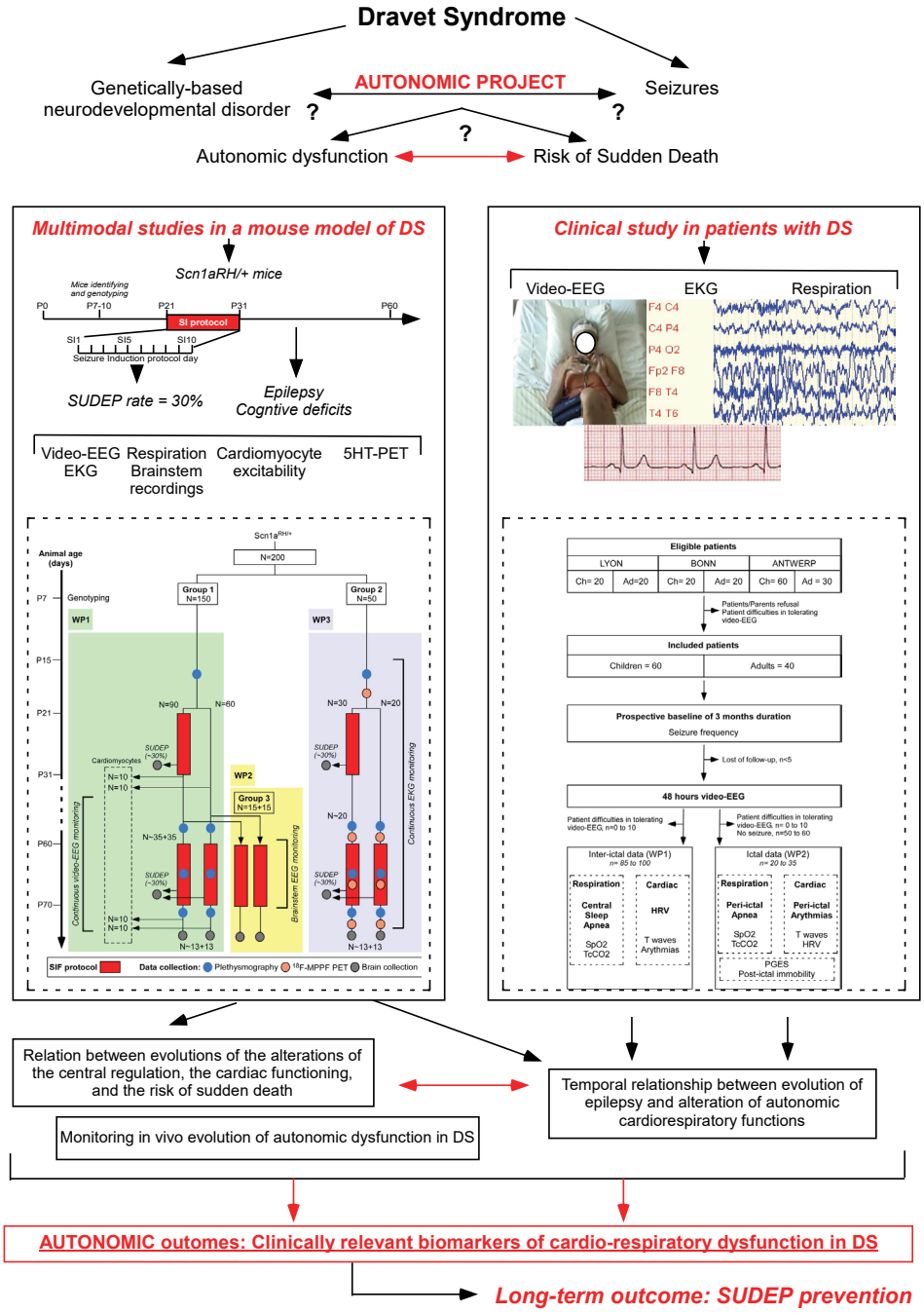
Massimo Mantegazza, Institute of Molecular and Cellular Pharmacology (IPMC, CNRS UMR7275 and University Côte d'Azur), Nice, France

Dravet syndrome (DS) is a rare and orphan genetic neurodevelopmental disease. The disease typically begins before the age of one with convulsions, and evolves into a combination of severe drug-resistant epilepsy and cognitive impairment. The risk of sudden epileptic death (SUDEP) is particularly high, regardless of the age or expression of the disease. There is no preventive treatment of SUDEP. SUDEP is a sudden and unexpected death after an epileptic seizure and is the consequence of a cardiorespiratory arrest precipitated by a seizure. However, as the genetic disease in DS can affect the heart and other vegetative functions, the relationship between the effect of the repetition of seizures and the effect of the genetic disease, per se, is poorly understood. No study has ever evaluated this in detail, and a better understanding of these relationship is needed to develop ways to prevent SUDEP and to better inform patients and their families about the risk of SUDEP.

We will study in 100 patients, by means of 48-hour video-EEG, several parameters of the cardiac rhythm and of respiration during wakefulness and sleep. We aim to analyse if the latter, especially abnormal regulation of cardiac rhythm during the night and/or occurrence of central sleep apneas are related to the age of the patients, the epilepsy duration and the frequency of the seizures. Because DS starts in children but then evolves along lifetime, it is important to conduct the study in children and in adults. The use of a mouse model is particularly important as it will allow us to verify that the cardiac and respiratory abnormalities observed in patients are indeed associated with the risk of SUDEP. Furthermore, the mice will allows us to directly test whether the cardiorespiratory disorders in DS are exclusively related to seizures or whether the genetic disease plays a role.

Our project will primarily deliver clinically relevant biomarkers of cardio-respiratory dysfunction in DS. They will then be used in preclinical studies to investigate potential therapeutic targets with the best outcome measures before being use

to design a multi-centre trial of SUDEP prevention in DS. They may also be useful for improving seizure detection devices that are increasingly used, although still insufficiently accurate for certain seizure types.



Paola Bovolenta

Brain4Sight

Deconstructing gene regulatory networks for improving sight and brain disabilities

Project Coordinator:

Paola Bovolenta, Centro de Biologia Molecular Severo Ochoa (CSIC-UAM) Universidad Autonoma de Madrid, Madrid, Spain

Project Partners:

Michèle Studer, iBV - Institut de Biologie Valrose, INSERM U1091, CNRS UMR7277, Nice, France

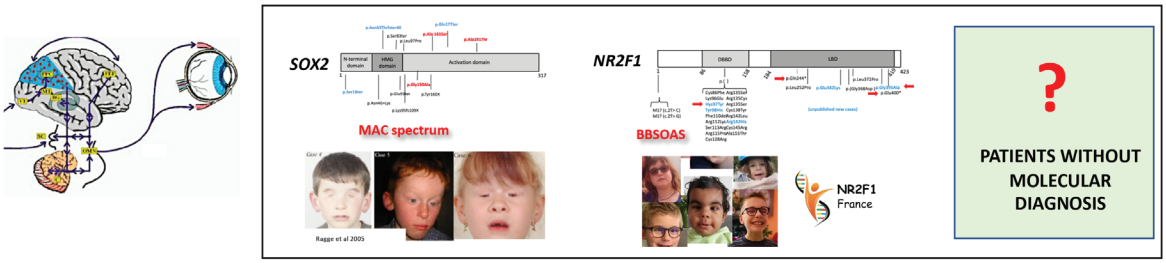
Silvia Russo, Istituto Auxologico Italiano, Laboratorio Biologia Molecolare, Milan, Italy

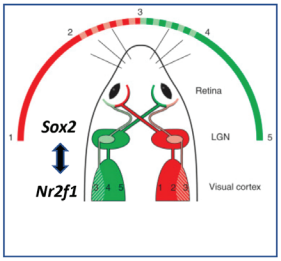
Benedikt Berninger, Adult Neurogenesis and Cellular Reprogramming, Institute of Physiological Chemistry, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany

Neuro-Developmental Visual Disorders (NDVD) are complex conditions caused by mutations in genes instructing cells on how to build an eye or other brain areas involved in vision. NDVD arise mostly during embryogenesis, are highly debilitating and variable disorders and often occur together with other neurodevelopmental disorders (NDD) such as intellectual disability, autism or epilepsy. This phenotypic variability severely hampers clinical diagnosis, disease management and delays possible alleviating therapies, creating practical and emotional burden to clinicians, patients and their families. Unfortunately, to date, there is only poor understanding of how mutations in a single gene can cause such a bewildering variability of clinical manifestations, as well as why the same mutation can have unique effects in different patients. The Brain4Sight consortium, composed of clinicians and basic researchers, seeks to unravel the reasons behind this understudied variability, focusing on the SOX2 and NR2F1 genes. These genes are, respectively, responsible for syndromic anophthalmia/microphthalmia and Bosch-Boonstra-Schaaf Optic Atrophy syndrome (BBSOA). To reach its goal, Brain4Sight will employ state-of-the-art genomic and sequencing technologies, human retinal and brain organoids derived from patients´ blood cells, which should closely mimic the processes that fail during individual human organ formation, as well as mouse models that reproduce human pathologies to address the complex issue of how such mutations make brain assembly go awry. Brain4Sight will thereafter use this new knowledge to restore genetic programs and reprogram brain cells to regenerate the cells most severely affected by the mutations, with the long-term goal to restore vision. Brain4Sight will thus provide fundamental knowledge towards improving diagnosis, management, prognosis and therapeutics for NDVD, in particular, and for NDD in general.

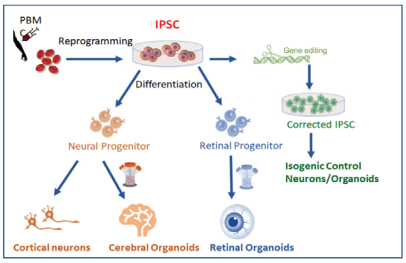
Deconstructing gene regulatory networks for improving sight and brain disabilities

Brains4Sight

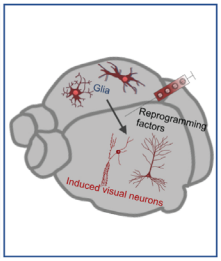




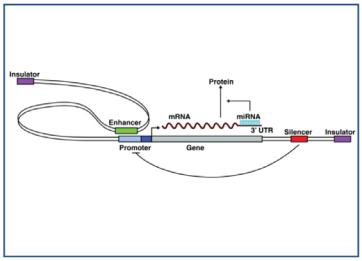
Aim 1: *Sox2 and Nr2f1 tissue specific interaction and function in the mouse VS*



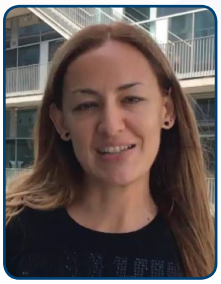
Aim 3: *Challenging SOX2 and NR2F1 mutations using human organoids*



Aim 4: *Generation of visual neurons by cell reprogramming*



Aim 2: *Discovering new variants in regulatory elements linked to the SOX2 gene*



Elena Martín García

CANSHANK

Involvement of the insula in the Autism neurodevelopmental disorder

Project Coordinator:

Elena Martín García, Dept de Ciències Experimentals i de la Salut (DCEXS), Universitat Pompeu Fabra (UPF), Parc de Recerca Biomèdica de Barcelona (PRBB) Barcelona, Spain

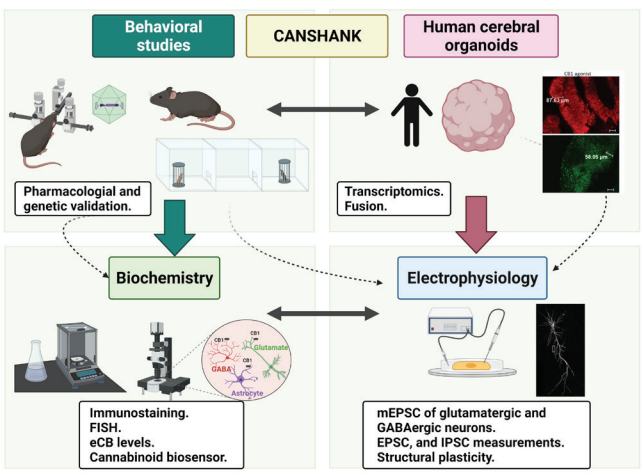
Project Partners:

Beat Lutz, Leibniz Institute for Resilience Research (LIR) gGmbH, Mainz, Germany

Michael Schmeisser, University Medical Center of the Johannes Gutenberg-University, Institute for Microscopic Anatomy and Neurobiology, Mainz, Germany

Giovanni Marsicano, INSERM U 1215, Neurocentre Magendie, Bordeaux, France

We will explore the pathophysiological mechanisms underlying autism spectrum disorder (ASD). ASD is a multifactorial complex disorder involving multiple genes, environmental factors, and the interaction among these factors. We will focus our attention on the involvement of a neuromodulatory system, the endogenous cannabinoid system, in specific cell types of a crucial brain region that represents a hub of communications, the insular cortex. We will use a well-recognized genetic mouse model of ASD, the deletion of the Shank3 gene, and several complementary experimental approaches: additional genetic mouse models, behavioral and electrophysiological techniques, viral vector strategies to express and delete some genes in specific cell types in the brain, strategies to investigate the use and the transformation of energy at the cellular level and human cerebral organoids. These techniques will provide important information to clarify the specific mechanisms underlying ASD. We hypothesize that the genetic deletion of Shank3 makes an imbalance of the insular endocannabinoid system signaling in specific cell types in a vulnerable period during neurodevelopment. These alterations seem responsible for the onset of neurodevelopmental alterations leading to ASD and the different symptoms of this disorder. We are a consortium with all the tools and expertise to successfully achieve our proposed objectives. Our research will have uniqueness and will result in a deeper understanding of the brain mechanisms involved in the onset and development of ASD. The inclusion of human organoids mimicking this neurodevelopmental disorder and the interaction with a SHANK3 haploinsufficiency/ Phelan McDermid patient organization will provide high translational value to our proposal. Our elucidation of novel mechanisms will deliver novel insights to shed light on innovative therapeutical approaches.



Alberto Bacci

DevInDS

Development of over-inhibition of cortical circuits in Down syndrome (DevInDS)

Project Coordinator:

Alberto Bacci, ICM - Institut du Cerveau | Paris Brain Institute, Sorbonne Université, CNRS, INSERM, Groupe Hospitalier Pitié Salpêtrière, Paris, France

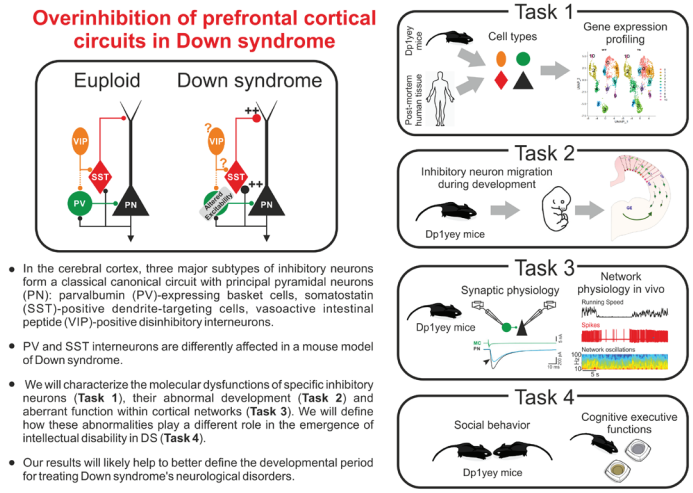
Project Partners:

Yann Herault, Université de Strasbourg, CNRS, INSERM, Institut de Génétique Biologie Moléculaire et Cellulaire, IGBMC, Strasbourg, France

Patrícia Espinheira de Sá Maciel, Universidade do Minho, Escola de Medicina, Campus de Gualtar, Braga, Portugal

Holger Heyn, Centro Nacional de Análisis Genómico (CNAG-CRG), Barcelona, Spain

Down syndrome (DS) is a developmental disorder caused by the presence of an extra copy of human chromosome 21 (Hsa21) and is characterized by various physical and neurological features, including intellectual disability and autism spectrum disorder. Recent research, including our work, suggests that intellectual disability of DS subjects might result from an over-inhibition of cortical networks. Cortical inhibition originates from a rich diversity of inhibitory neuron subclasses, which operate a fine division of labor during brain activity responsible for cognitive functions. We hypothesize that specific developmental alterations of distinct inhibitory circuits of the prefrontal cortex underlie cognitive and sociability deficits in DS. We will characterize the molecular dysfunctions of specific inhibitory neurons, their abnormal development and aberrant function within cortical networks. We will define how these abnormalities play a different role in the emergence of intellectual disability in DS.



- In the cerebral cortex, three major subtypes of inhibitory neurons form a classical canonical circuit with principal pyramidal neurons (PN): parvalbumin (PV)-expressing basket cells, somatostatin (SST)-positive dendrite-targeting cells, vasoactive intestinal peptide (VIP)-positive disinhibitory interneurons.
- PV and SST interneurons are differently affected in a mouse model of Down syndrome.
- We will characterize the molecular dysfunctions of specific inhibitory neurons (**Task 1**), their abnormal development (**Task 2**) and aberrant function within cortical networks (**Task 3**). We will define how these abnormalities play a different role in the emergence of intellectual disability in DS (**Task 4**).
- Our results will likely help to better define the developmental period for treating Down syndrome's neurological disorders.

This consortium combines a multi-scale, interdisciplinary approach: cellular and molecular biology, neurophysiology, genetics and behavioral analyses in mouse models. Importantly, we will also use neuropathology and molecular and cell biology in human tissue. This consortium will strongly benefit from the close collaboration with Dr. Marie-Claude Potier (ICM, Paris, France) and Dr. Mara Dierssen (CNAG-CRG, Barcelona, Spain).

We expect to provide a first detailed investigation of neuronal/cellular mechanisms that may underlie cognitive abnormalities of DS, paving the way for novel therapeutic interventions, essential to help DS individuals to live an adequate independent life. Importantly, unexpected results originating from research programs like this, will also advance our knowledge on the mechanisms underlying brain function.

Andreas Reif

DynAMoND

Dynamics of Affect Modulation in Neurodevelopmental Disorders

Project Coordinator:

Andreas Reif, Dept of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt – Goethe University, Frankfurt am Main, Germany

Project Partners:

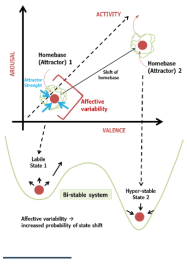
J. Antoni Ramos-Quiroga, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain

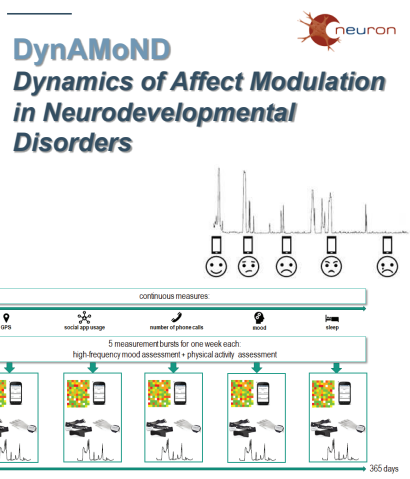
Giovanni de Girolamo, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

Jan Haavik, University of Bergen, Bergen, Norway

Nader Perroud, University Hospitals of Geneva, Geneva, Switzerland

Classification of psychiatric disorders is mainly based on clinical observations and scientific traditions. Such traditions have resulted in diagnostic systems where even conditions that appear to share many symptoms and risk factors are considered distinct categories. In the DynAMoND project we are comparing three such psychiatric diagnoses, i.e., ADHD, bipolar disorder, and borderline personality disorder. These conditions have traditionally been studied separately within the fields of child psychiatry, adult psychiatry, and personality disorders, respectively. All three disorders are characterized by excessive mood fluctuations that may last for hours, days or months. These mood swings, also termed emotional instability, are distressful for patients and may be difficult to treat. Still, we do not know whether the nature of these mood swings is similar across the disorders, or different. DynAMoND is a collaborative study performed in Germany, Spain, Switzerland, Norway and Italy that will explore emotional fluctuations in these disorders across traditional boundaries. We will include patients suffering from ADHD, bipolar disorder or borderline disorder as well as healthy controls (120 each, from 14 to 30 years of age). We will use data from smartphones and their inbuilt sensors, as well as data from online surveys, to collect information about mood, activity, and stress. Participants will also provide saliva samples for genetic studies. Data from questionnaires will be taken at the beginning of the study. At the end of the study, patients will receive a summary about findings, the main outcomes, and actionable recommendations. If successful, the project may lead to improved treatment, less burden of disease and improved quality of life for large groups of patients.





Andre Fischer

EPINEURODEVO

Patient-centered Targeting of Epigenetic Vulnerabilities in Neurodevelopmental Disorders: A Cross-disciplinary Platform for Druggable Disease Models

Project Coordinator:

Andre Fischer, University Medical Center Göttingen, Göttingen, Germany

Project Partners:

Guiseppe Testa, European Institute for Oncology (IEO), Milan, Italy

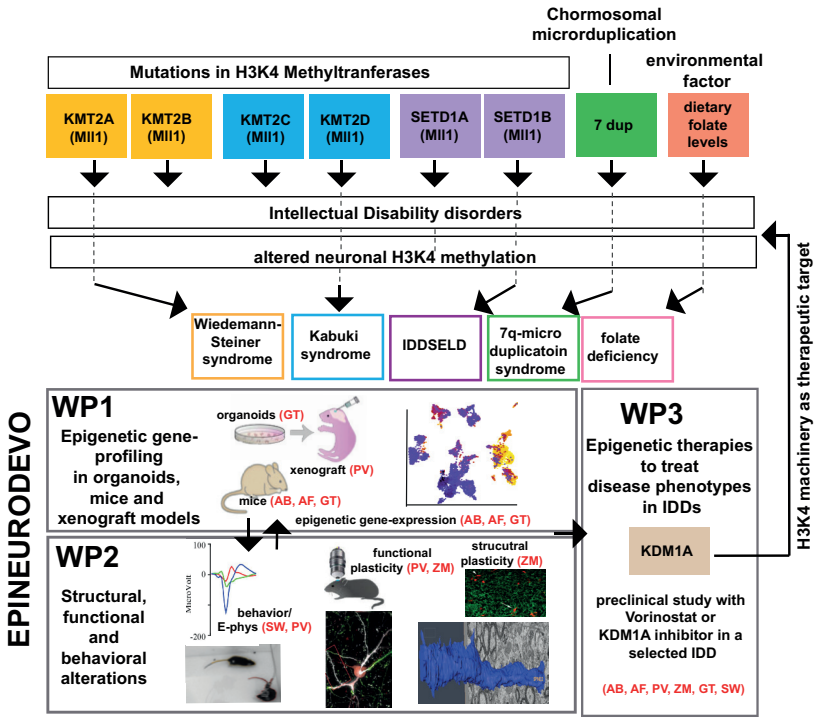
Angel Barco, Universidad Miguel Hernández, Elche, Spain

Shlomo Wagner, University of Haifa, Haifa, Israel

Pierre Vanderhaeghen, VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium

Zoltán Mészár, University of Debrecen, Debrecen, Hungary

Intellectual disability disorders (IDDs) are a group of devastating disorders that lead to learning impairment and behavior defects in young children. They are mainly caused by mutations in single genes. Many of these genes encode for proteins that control the process of epigenetic gene-expression such as the methylation of histone proteins. Of particular importance in this context are the proteins that orchestrate the methylation of histone 3 at lysine residue 4 (H3K4me), since mutation in any of these genes cause IDDs. Our overarching aim is to better understand the de-regulation of H3K4 methylation in IDDs. We will perform a systematic analysis in the developing and adult brain across the spectrum of IDDs. Here, we build on the unique expertise of our consortium in epigenetics, brain development, neuronal structural and functional plasticity with ample experience in modeling IDDs in mouse models, iPSC derived human brain organoids and xenograft models. Our results will provide a blueprint for translation research in neurodevelopmental diseases. Since we also plan to test therapeutic strategies, our research could have immediate clinical impact.



Initials refer to the partners contributing to the specific work packages

Jaan-Olle Andressoo

GDNF UpReg

Glial Cell Line-Derived Neurotrophic Factor (GDNF) modulating schizophrenia: a promising target for innovative treatment

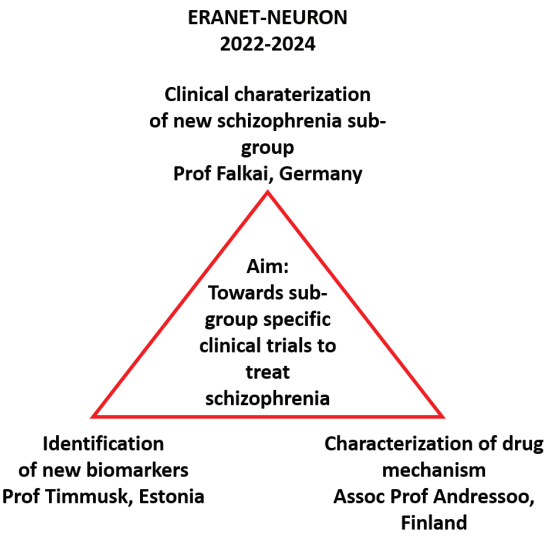
Project Coordinator:

Jaan-Olle Andressoo, Dept of Pharmacology, Faculty of Medicine, University of Helsinki, Helsinki, Finland

Project Partners:

Peter Falkai, Ludwig-Maximilians-Universität München, Dept of Psychiatry and Psychotherapy, Munich, Germany

Tönis Timmusk, Protobios Ltd, Estonia



Schizophrenia affects about 1% of the population and often requires lifelong treatment. However, currently available treatments can alleviate only a fraction of the symptoms, often at the cost of severe side-effects. It is increasingly clear that "one-size matches all" treatment does not exist, as patients respond differently to existing treatments. Thus, highlighting a need for understanding the mechanisms that underlie the differences between patients groups to enable design of individual more personalized treatments.

The Andressoo team has very recently made substantial progress in that direction by studying how a protein called glial cell-line derived neurotrophic factor (GDNF) can influence the disease. By implementing the uncovered mechanism, Andressoo team was able to create an animal model of schizophrenia, which, in turn, allowed identification of a drug that can reverse the disease in an animal model. This drug is already in clinical use, but is used for different purpose. Importantly, reprofiling of an existing drug for the treatment of another disease is relatively easy, fast and cost-effective, when compared to the development of new drugs. However, to proceed to clinical trials, better patient characterization, stratification and understanding on the drug's action is required.

This project brings together clinical experts Dr Peter Falkai (GE), a biotechnology company to create better tests for analysing patient sub-groups (Protobios/ Dr T. Timmusk, EST) and pre-clinical analysis expert (Dr J.O. Andressoo, FI) to build information needed for designing clinical trials in the near future.

Camilla Bellone

InflASD

Physiological and molecular effects of inflammation on the severity of Shank3-based ASD phenotype on mouse and hPSC model

Project Coordinator:

Camilla Bellone, Dept Basic Neuroscience, University of Geneva, Geneve, Switzerland

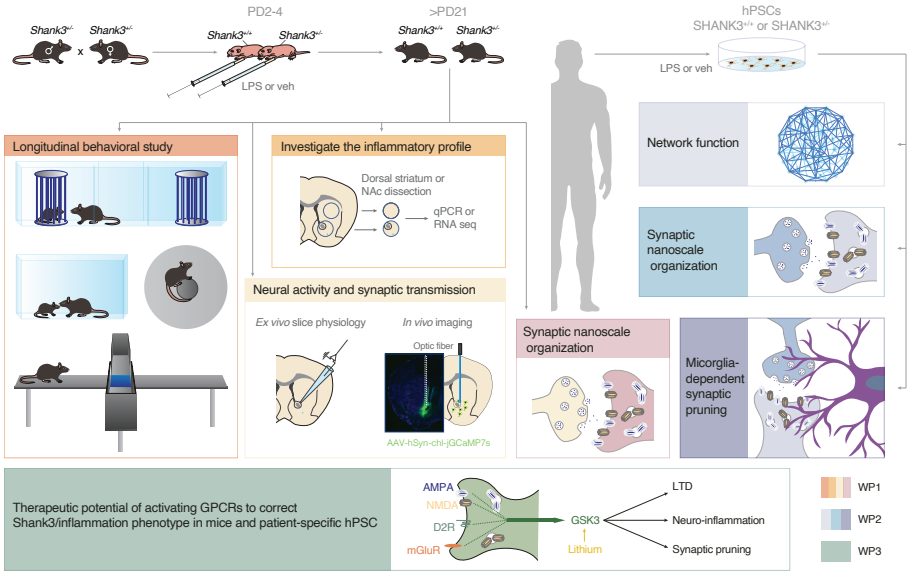
Project Partners:

Eric Hosy, Institut Interdisciplinaire de Neurosciences CNRS UMR 5297 Université Bordeaux, Bordeaux, France

Michela Matteoli, Laboratory of Pharmacology and Brain Pathology Humanitas Clinical and Research Centre, Milan, Italy

Oliver Brüstle, Institute of Reconstructive Neurobiology, Universitaetsklinikum Bonn, Bonn, Germany

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by impairments of social interaction and communication accompanied by a pattern of repetitive and restrictive behaviours. Since several autism risk genes affect the function of specialized structures that allow the communication between neurons, studies in the last few years suggest that pathogenesis of ASD may be attributed to deficits in synaptic function. Mutations in the SHANK3 gene, coding for a scaffolding protein located at excitatory synapses, account for 1-2% of all ASD cases. Although autistic phenotype has been described across individuals with SHANK3 deficiency, heterogeneity in the severity of the phenotype has been reported.



Here we hypothesize that this phenotype heterogeneity is the consequence of the interplay between genetic and environmental factors (double-hits). Using human pluripotent stem cells differentiated into neurons or microglia, and exploiting genetic/environmental double hit mouse models we will identify the mechanisms underlying inflammation/gene interaction. The ultimate goal of InflASD is also to identify new strategies to treat ASD by controlling the spectrum of the inflammatory responses affecting the severity of the phenotype.

Takashi Namba

MEPIcephaly

Metabolic and epigenetic interplay in neural progenitor cells: investigating neurodevelopmental disorders associated with impaired neural progenitor cell expansion

Project Coordinator:

Takashi Namba, Neuroscience Center, HiLIFE - Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland

Project Partners:

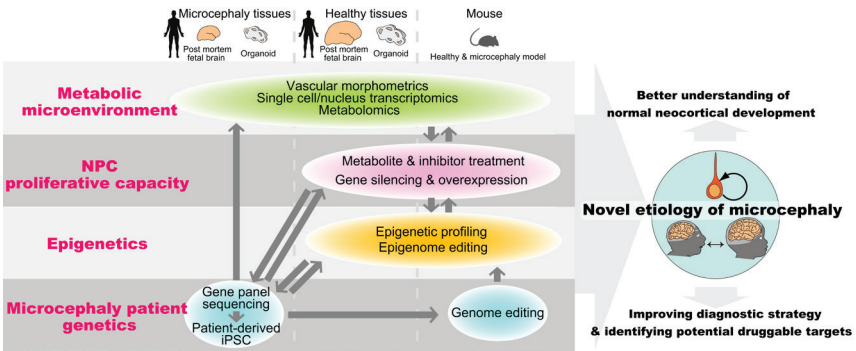
Peter Carmeliet, Laboratory of Angiogenesis & Vascular Metabolism, Center for Cancer Biology (CCB), VIB-KU Leuven, Leuven, Belgium

Mareike Albert, Center for Regenerative Therapies TU Dresden (CRTD), Technische Universität Dresden (TUD), Dresden, Germany

Jeannette Nardelli, Inserm U1141, Robert Debre Hospital, Paris, France

The size of the brain matters for its functional capability. Having an abnormally small brain, referred to as microcephaly, may lead to mental impairments and motor disabilities. An abnormally small brain may result from insufficient numbers of neurons produced during fetal brain development, often caused by the inadequate expansion of neural progenitor cells. Currently, our knowledge about the mechanistic causes of microcephaly is far from complete, leaving a large proportion of microcephaly patients without a genetic diagnosis. Lack of early diagnosis limits the options for early intervention and counseling of affected families.

We have recently discovered that metabolic regulations are important for the adequate expansion of neural progenitor cells during fetal development. Based on our findings, this project aims to further explore the metabolism of progenitor cells in normal and diseased conditions, seeking to better understand the causal relationship between abnormal neural progenitor cell metabolism and microcephaly. This project will investigate important metabolic pathways and their link with epigenetics – a layer of information on top of our genome that affects which genes are expressed by a given cell type. We will study how the metabolic-epigenetic interplay regulates gene expression during neural progenitor cell expansion. Finally, we aim to identify novel causative metabolic genes of microcephaly. This project will provide new insights into the causes of microcephaly, which is key for the development of improved diagnostic tools, treatment options and preventive care.



Tarja Malm

MINERVA

Microglia/neuron crosstalk in autism spectrum disorder: Role of early inflammatory activation

Project Coordinator:

Tarja Malm, University of Eastern Finland, A.I.Virtanen Institute for Molecular Sciences, Finland

Project Partners:

Markus Wöhr, KU Leuven, Faculty of Psychology and Educational Sciences, Research Unit Brain and Cognition, Leuven, Belgium

Carsten Culmsee, Philipps-University of Marburg Faculty of Pharmacy, Institute for Pharmacology and Clinical Pharmacy, Marburg, Germany

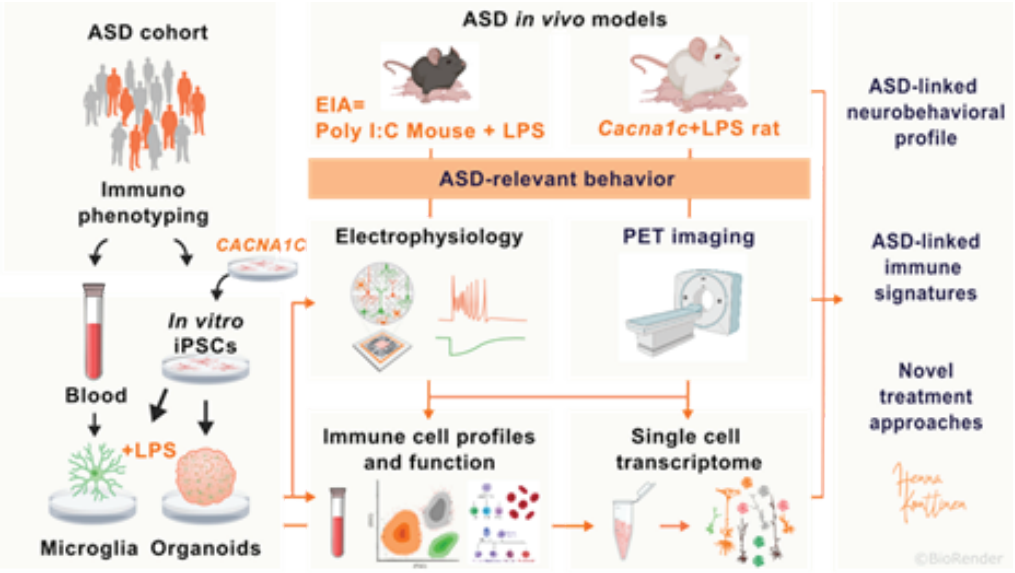
Judith Alferink, Dept of Mental Health, University Hospital of Münster, Münster, Germany

Laura Ricceri, Centre for Behavioural Sciences and Mental Health, Istituto Superiore di Sanità, Rome, Italy

The goal of MINERVA is to understand how the immune system and genetic risk factors influence the activity of immune cells in the brain, the microglia, and their communication with neurons, and how these processes modulate neurodevelopmental alterations and the severity of autism spectrum disorder (ASD). The results of these studies will help to better understand the mechanisms of the immune system that are associated with ASD development and behavioral impairment. In addition, based on these results, innovative therapeutic approaches may be developed that target neuro-immune and behavioral deficits in ASD. In particular, we apply 3D-organoid cultures containing neurons and microglia, which are obtained from patient-derived stem cells, to investigate the close interplay between the immune cells and the neurons for development of a human neuronal network in a dish. Further, we investigate the effects of immune stimulation on early brain development and behavioral alterations in rodent models relevant to ASD. Comparing immune and metabolic signatures in the animal and cell models with ASD-patient samples, will allow evaluation of the potential translation of the data obtained in the experimental settings to the clinic, including potential therapeutic approaches.

We hypothesize that genetic risk factors, especially Cacna1 mutations, accelerate bioenergetic dysfunction and persistent pro-inflammatory activation of microglia and peripheral immune cells, which further drive malfunction in the microglia-neuron interaction and propagate the impact of maternal infections on E/I imbalance in the developing brain. This leads to sustained, lifelong consequences in modulating ASD phenotype and disease severity. We utilize samples, cells and clinical data from individuals with ASD and state-of-the-art human-based in vitro and in vivo models

to discover the molecular underpinnings of ASD and test potential treatment approaches. Combination of in vivo models, human cells and human-based 3D cerebral organoids provide an innovative international collaboration platform to discover disease mechanisms and test novel therapeutics that translate back to the clinic.



Impact : Novel therapeutic mechanisms // validation of novel innovative and translational models // Promotion of meaningful ASD patient involvement //Dissemination and communication

Stéphanie Baulac

MOSAIC

Molecular and circuits bases of epileptogenic mosaic cortical malformations

Project Coordinator:

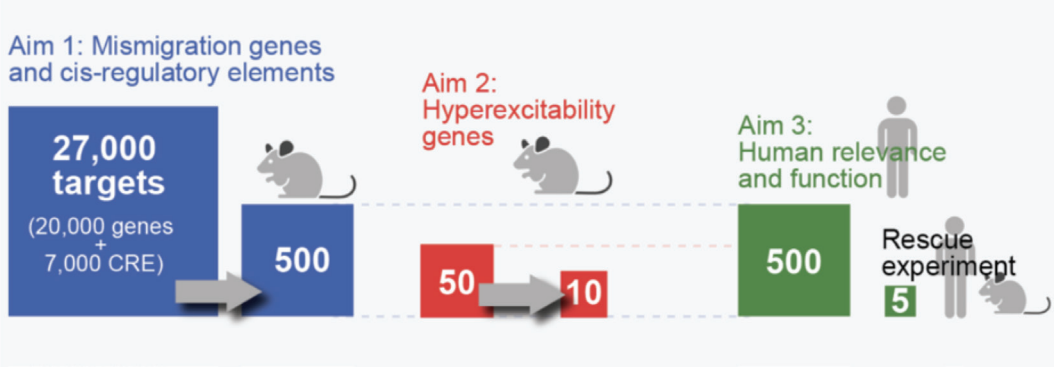
Stéphanie Baulac, Paris Brain Institute, Inserm, Sorbonne Université, Paris, France

Project Partners:

Denis Jabaudon, Dept of Basic Neurosciences, University of Geneva, Geneva, Switzerland

Boyan Bonev, Helmholtz Pioneer Campus, Helmholtz Zentrum, Neuherberg, Germany

The human brain is a genetic mosaic resulting from frequent somatic mutations during development. Somatic mosaicism can cause Focal Cortical Dysplasia (FCD), a cortical malformation that manifest in young children as drug-resistant focal seizures amenable to surgery resection. FCD are characterized by cortical disorganization secondary to abnormal migration and differentiation of neurons. Brain somatic mutations in genes of the mTOR signaling pathway are a frequent cause of FCD; however genetic etiology remains unidentified in many cases. Our consortium aims at understanding the genetic, molecular and circuit bases of FCD by combining in vitro and in vivo approaches in mouse and human. In Aim 1, using an in vivo genome-wide screen, we will identify genes and enhancers involved in neuronal mismigration in the mouse neocortex. In Aim 2, we will functionally investigate how candidate may cause abnormal circuit activity and seizures. In Aim 3, we will identify mosaic somatic mutations in a patient cohort and use human iPSCs-derived cortical organoids to identify the developmental mechanisms at play in FCD. Hence, ultimately, this proposal will pinpoint potentially druggable targets for this childhood neurodevelopmental disorder.



Elisenda Eixarch

MULTI-FACT

Multi-centric study of Fetal Abnormal Cortical Trajectory with standardised and privacy-preserving method on fetal MRI

Project Coordinator:

Elisenda Eixarch, Fetal Medicine Research Center, BCNatal (Hospital Clínic and Hospital Sant Joan de Déu), University of Barcelona; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona and Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain

Project Partners:

Meritxell Bach Cuadra, CIBM Center for Biomedical Imaging, Lausanne University (UNIL) and University Hospital (CHUV), Lausanne, Switzerland

Guillaume Auzias, Institut de Neurosciences de la Timone UMR 7289, Aix-Marseille Université, CNRS, Marseille, France

Gemma Piella, Barcelona Centre for New Medical Technologies (BCN MedTech), Dept of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain

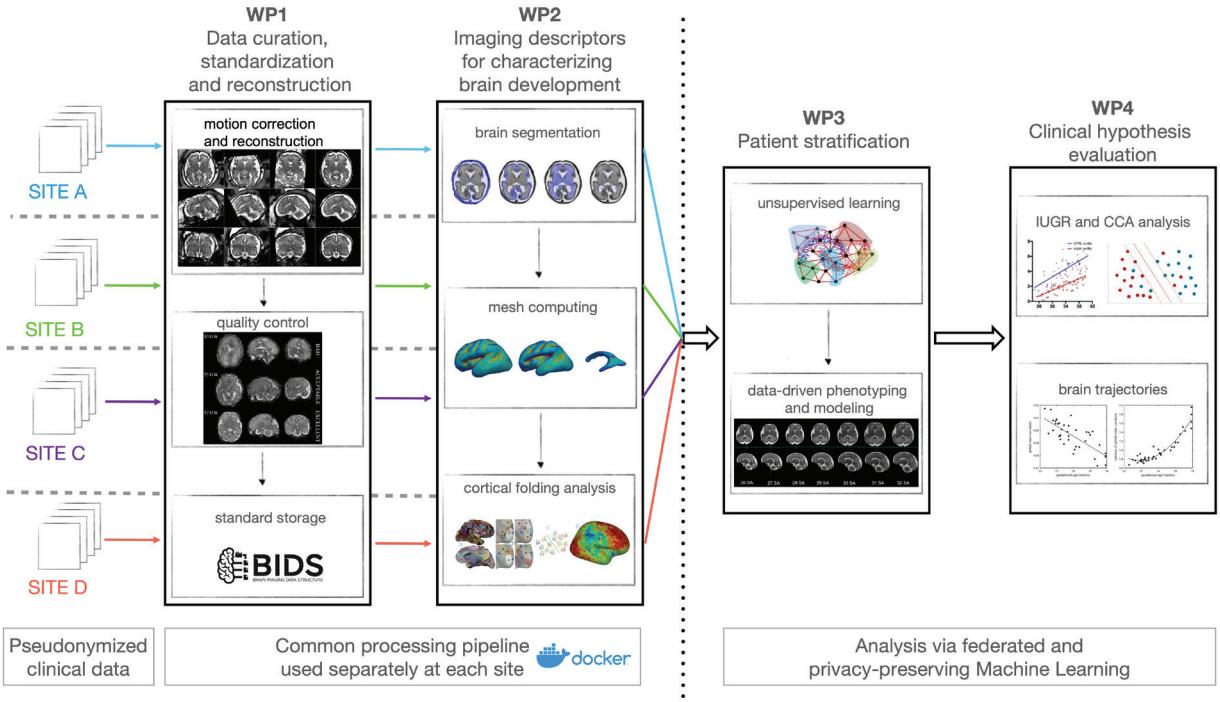
Daniel Rueckert, Klinikum rechts der Isar der Technischen Universität München, München, Germany

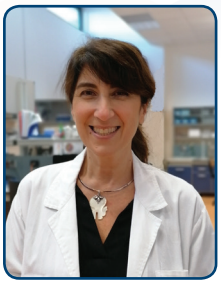
We increasingly understand the impact that dissimilar development of the brain before birth may have on people. Around 10% of children do not follow the usual path of brain development when they are in the womb, which can cause disabilities and make their lives more difficult. It could be possible to identify two out of three of these children using scans before they are born, but currently their issues are usually only discerned later in life. This means that they cannot receive the extra help they need when they are very young, making it harder to improve their lives when they are older. This project wants to change that by increasing the understanding of brain development in unborn babies and finding features, called biomarkers, which can alert us to future problems they might have.

Looking at babies' brains during pregnancy helps doctors decide how to treat their patients, both the mothers and unborn children. We already know that using magnetic resonance imaging (MRI) to check the brains of fetuses is safe and lets us see the brain better than ultrasound images. However, MRI, which uses magnetic fields and radio waves to create images of the body, has been improved over the years for adults, but the same improvements are still yet to be made for fetuses. This is exactly what this project hopes to do for the first time, by bringing together many experts in different fields and from different hospitals to work together in a new and collaborative way.

We will examine two conditions that can affect unborn children to develop our tools.

The first is intrauterine growth restriction, which affects one in ten pregnancies. This is where the unborn baby does not get what it needs to grow well. The second is corpus callosum agenesis, which is rare. In this condition the part of the brain that links its two halves does not grow properly. We will create new technologies to follow more than 950 unborn babies with these conditions and utilise our new understanding to make tools that can be used around the world to find many more babies whose brains are not developing normally before they are born, and help them to have a better future.





Enza Maria Valente

NDCil

Neurodevelopmental ciliopathies: a multimodel approach from molecular mechanisms to patients variant interpretation and treatment strategies

Project Coordinator:

Enza Maria Valente, Neurogenetics Research Centre, IRCCS Mondino Foundation, Pavia, Italy

Project Partners:

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Oliver Blacque, School of Biomolecular and Biomedical Science, University College Dublin, Dublin, Ireland

Marius Ueffing, Institute for Ophthalmic Research, Dept for Ophthalmology, University of Tübingen, Tübingen, Germany

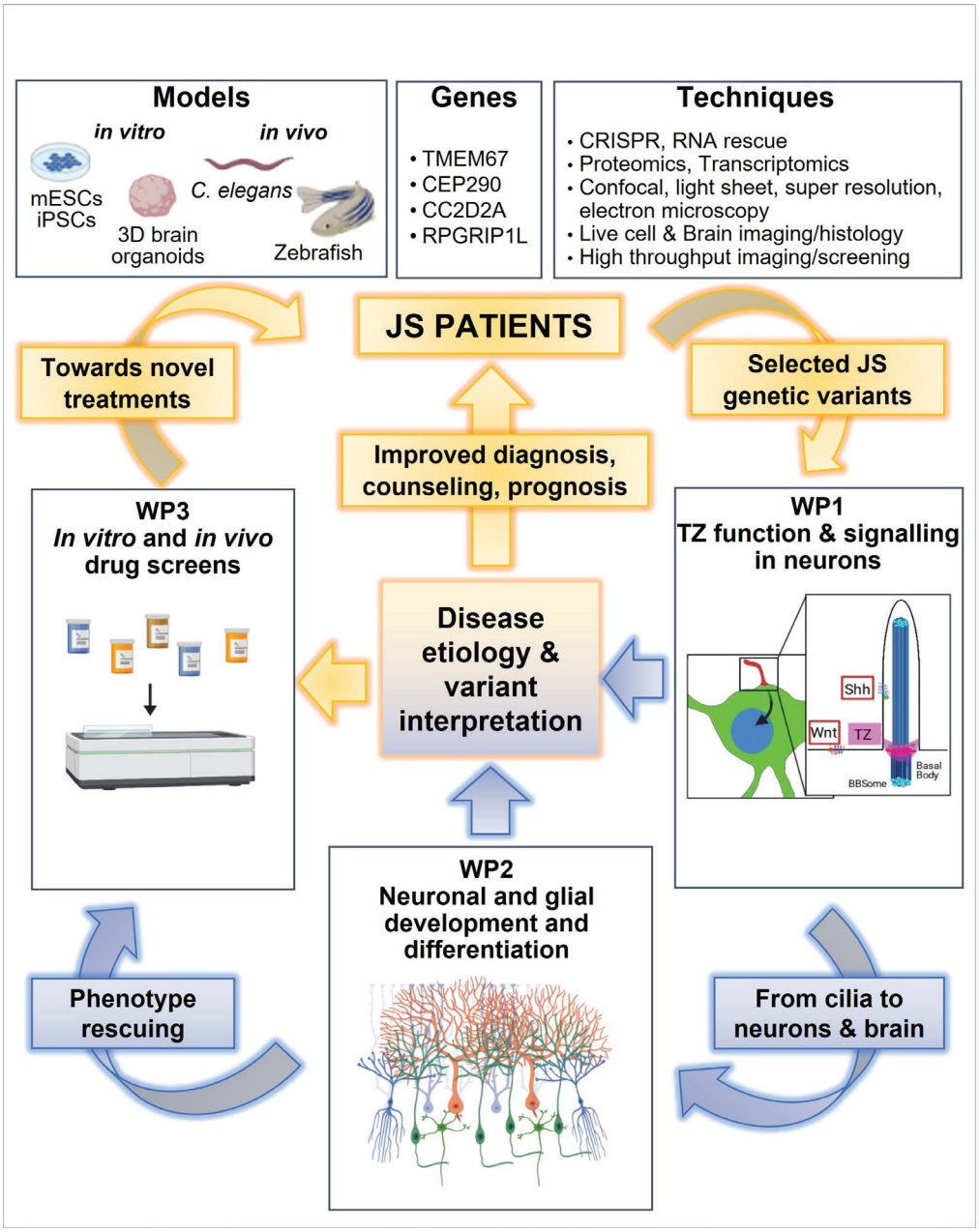
András Dinnyés, BioTalentum Ltd., Gödöllő, Hungary

Nervous system malformation and neurodevelopmental defects (ND) are common hallmark features of genetically inherited diseases called ciliopathies. All ciliopathies are caused by abnormalities in tiny hair-like extensions called primary cilia (Cil), which are found on the surface of most cell types, including neuronal and glial cells. These cilia act as antennae that allow cells to communicate with each other so that they can coordinate their behaviours to form fully functional tissues and organs. Whilst much progress has been made in understanding cilia biology, surprisingly, we know very little about how they build and maintain the nervous system, and there are no therapeutic strategies to resolve the neurodevelopmental features of disease. Furthermore, how mutations in ciliopathy patients specifically affect underlying cilia genes are poorly understood.

To address these shortfalls, the NDCil project focusses on the most prominent neurodevelopmental ciliopathy called Joubert Syndrome (JS). Patients with this disease are born with malformation of cerebellar and brainstem structures, resulting in debilitating brain dysfunction. Research thus far has found that JS disease disrupts processes at the base of the ciliary rod called the transition zone. The objectives of NDCil are to: i) uncover new fundamental knowledge of how JS affects the brain at different levels of scale (cilia/TZ, neuronal and glial cells, whole brain); ii) establish how mutations found in JS patients disrupt cilia genes and cell-cell communication; and iii) discover new drugs that alleviate JS symptoms. These objectives will be achieved using well-established and novel cell and animal models that mimic the JS disease state, including pluripotent stem cells from patients, mouse stem cells, zebrafish and the invertebrate animal C. elegans, together

with state-of-the-art techniques such as gene editing (CRISPR-Cas9), advanced imaging, automated drug screening and proteomics.

Altogether, our interdisciplinary consortium of five partners across five countries provides an integrated platform for determining precisely how JS affects neurons and the brain, and how mutations found in JS patients affect underlying genes. The project also strives to discover new potential lead compounds for JS resolution. We expect the project to have direct benefit to patient diagnosis, prognosis, counselling, and therapy. Also, we anticipate that many aspects of the research will be applicable to the wider group of neurodevelopmental disorders beyond JS.



Katharina von Kriegstein

ReDyslexia

Understanding and targeting developmental dyslexia: from animal models to humans

Project Coordinator:

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Project Partners:

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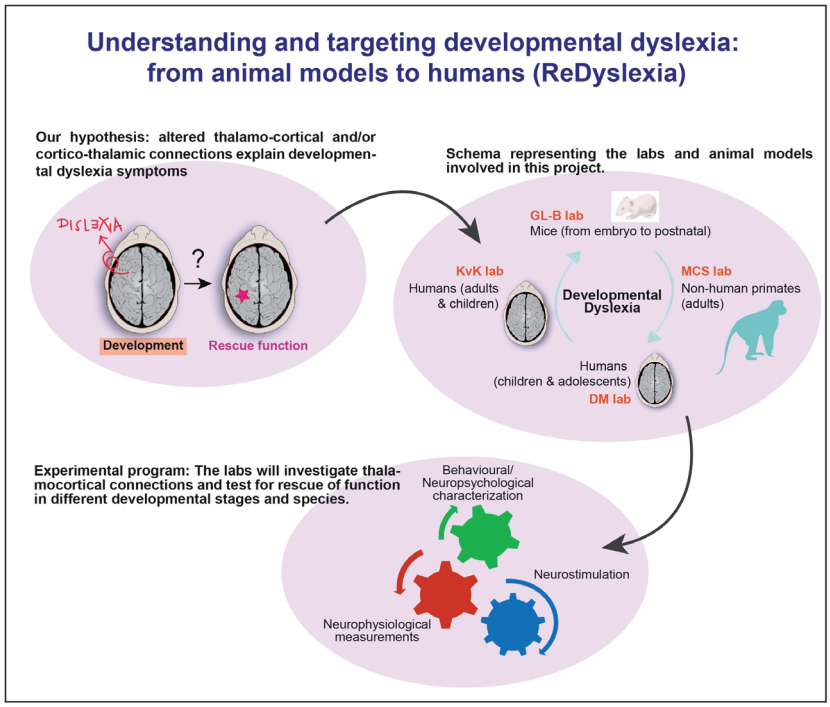
Michael C. Schmid, Faculty of Sciences and Medicine, University of Fribourg, Fribourg, Switzerland

Deny Menghini, Child and Adolescent Neuropsychiatry Unit, Dept of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Developmental dyslexia (DD) is a brain-based developmental disorder. It is characterized by severe impairments in reading in otherwise healthy individuals. DD occurs in 5-10% of children worldwide and persists into adulthood. Since reading is so fundamental for modern societies, individuals with DD are hindered both in school and in the workforce. DD has high societal costs. Current treatment of DD consists of time-consuming training with speech therapists and psychologists over several years. Development of effective treatment is urgently needed, but hampered by a lack of knowledge about the brain dysfunction causing DD. For decades, researchers have focused on explaining DD by dysfunctional mechanisms of the brain's language centres. Findings from our laboratories offer a novel perspective on DD that emphasises dysfunction of sensory pathways. Sensory pathways are structures that connect the eyes (and ear) with the rest of the brain to provide the sensory basis for reading. Motivated by our recent results, ReDyslexia will work for two major aims: (1) to better understand sensory pathway dysfunction in DD; (2) to directly use this knowledge for improving treatment strategies. To do that we combine experiments in two animal models (mice, monkeys) and studies in humans with DD at different developmental stages. Results from ReDyslexia will have direct implications for how DD is diagnosed and treated.



Arnaud Monteil

RestoreLeak

Accelerating Research on Neurodevelopmental Channelopathies: from Bench to Bedside

Project Coordinator:

Arnaud Monteil, Institute for Functional Genomics, CNRS UMR5203 - INSERM U1191, Montpellier, France

Project Partners:

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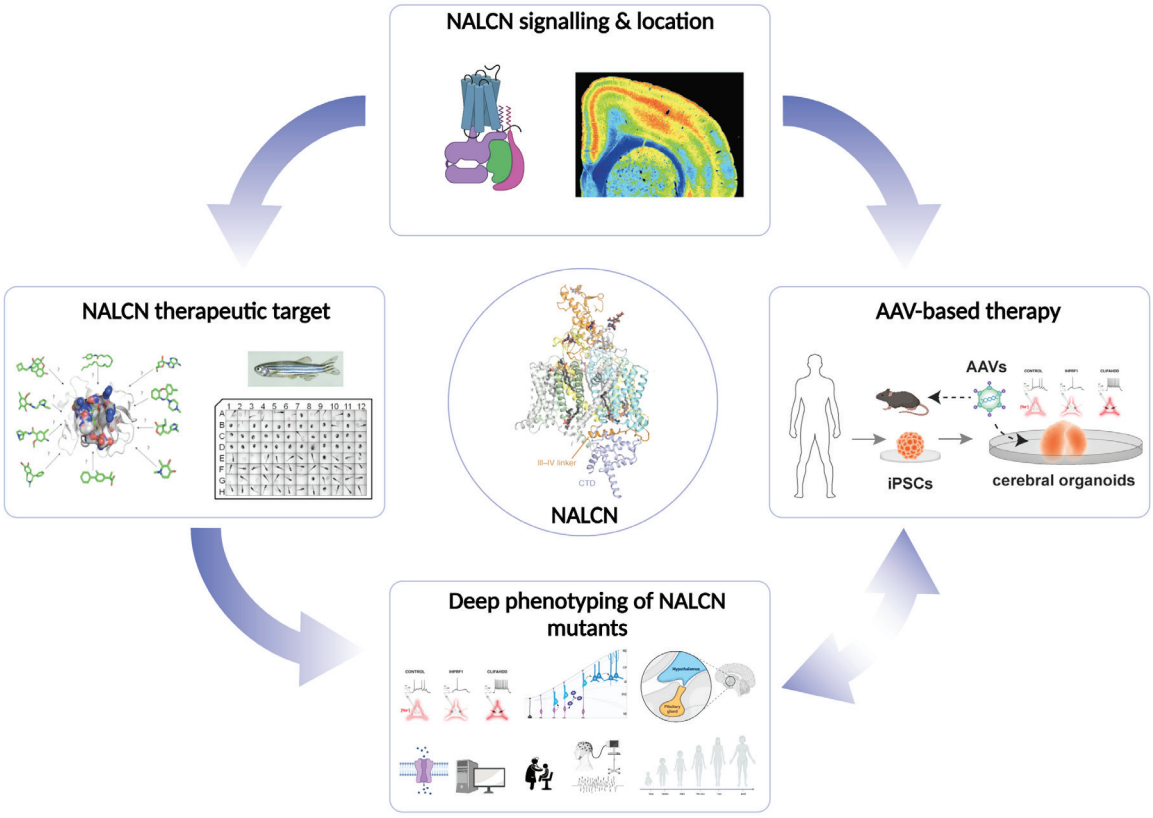
Antonio Gil-Nagel, Epilepsy Program, Neurology Dept, INCE Foundation, Ruber Internacional Hospital, Madrid, Spain

Leszek Lisowski, Laboratory of Molecular Oncology and Innovative Therapies, Military Institute of Medicine, Warsaw, Poland

Stephan Pless, Dept of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark

Several cell types, e.g., neurons and endocrine cells, exhibit electrical activity crucial for their physiological function. This electrical activity involves a complex interplay between different classes of specialized proteins. Any functional alteration of these proteins may, in humans, drive pathological states with devastating health consequences, including premature death. The present proposal focuses on the NALCN (Na+ leak channel) protein, a crucial regulator of cell electrical activity. Mutations in the NALCN gene were recently described in two ultra- rare and severe neurodevelopmental disorders referred to as the IHPRF1, for Infantile, Hypotonia, with Psychomotor Retardation and Characteristic Facies 1, inherited autosomal recessive syndrome affecting 40 patients from 23 families and the CLIFAHDD, for Congenital contractures of the Limbs and FAce, Hypotonia, and Developmental Delay, dominant syndrome which so far affects 45 patients with de novo mutations. Both syndromes display an onset early in infancy and may lead to premature death. The overall goal of the project is (i) to decipher molecular, cellular and circuit mechanisms involved in the etiology of these two pediatric diseases and (ii) to develop innovative and safe treatment options for patients. This will be achieved by (a) the combination of specific and complimentary know-hows and expertise from multiple laboratories across Europe, (b) the use of specific cell lines, patient cell derived preclinical models, such as induced pluripotent stem cells & brain organoids, and animal models. To maximize the chances of success, this project will rely on close collaboration between internationally recognized neuroscientists and neurologists in close association with the Libellas Foundation, a patient advocacy group (fundacionlibellas.org).


NALCN signalling & location
NALCN therapeutic target
AAV-based therapy
AAVs
iPSCs
cerebral organoids
III–IV linker
CTD
NALCN
Deep phenotyping of NALCN mutants

Alessandra Pierani

ROSSINI

peRsistence Of tranSient neuronS In Neurodevelopmental dIsorders

Project Coordinator:

Alessandra Pierani, Institut IMAGINE, Institute of PSYCHIATRY and NEUROSCIENCE of Paris, INSERM, Université de Paris, Paris, France

Project Partners:

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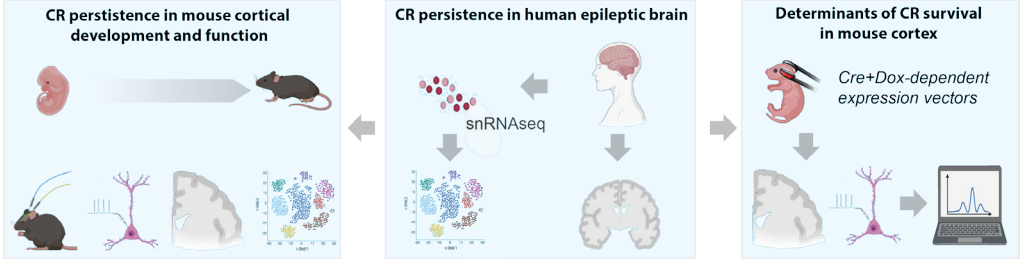
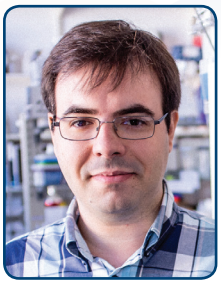
Liset M de la Prida, Instituto Cajal, CSIC, Madrid, Spain

Heiko J Luhmann, Institute of Physiology, Universität Mainz, Mainz, Germany

Eleonora Aronica, University of Amsterdam, Amsterdam, Netherlands

Neurodevelopmental disorders are disabilities involving brain dysfunction as a result of altered brain assembly during embryonic development. They include autism, attention-deficit/hyperactivity disorder, intellectual disability, cerebral palsy, and various forms of epilepsy. Understanding deficits involved in these disorders is of utmost importance in the search for therapeutic strategies to cure these patients. A variety of mechanisms may be involved in abnormal brain development, including the generation of neurons, their migration and their proper connections. In addition, a form of 'programmed cell death' is emerging as a novel, yet poorly studied, mechanism for proper brain development. Some neurons (including a group of neurons called 'Cajal-Retzius cells') appear transiently during brain development where they are involved in the construction of neural circuits and are programmed to die at the end of brain maturation. Aberrant survival of these neurons has been found in patients with neurodevelopmental disorders associated with epilepsy. Our teams have discovered that forcing just some of these neurons to survive after birth perturbs brain wiring, leading to aberrant brain activity and epileptic seizures. The ROSSINI project gathers European experts in brain development and function using complementary advanced techniques to study how the aberrant survival of Cajal-Retzius cells in mice and humans leads to altered brain activity in neurodevelopmental disorders. In this project, we aim to identify key mechanisms of 'programmed cell death' during brain development and evaluate its role in neurodevelopmental disorders associated with epilepsy, paving the way towards identification of novel targets or strategies for therapeutic intervention in these disorders.





João Peça

SHANKAstro

Astrocytes dysfunctions in Phelan-McDermid syndrome: from mechanisms towards new therapeutic strategies

Project Coordinator:

João Peça, Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal

Project Partners:

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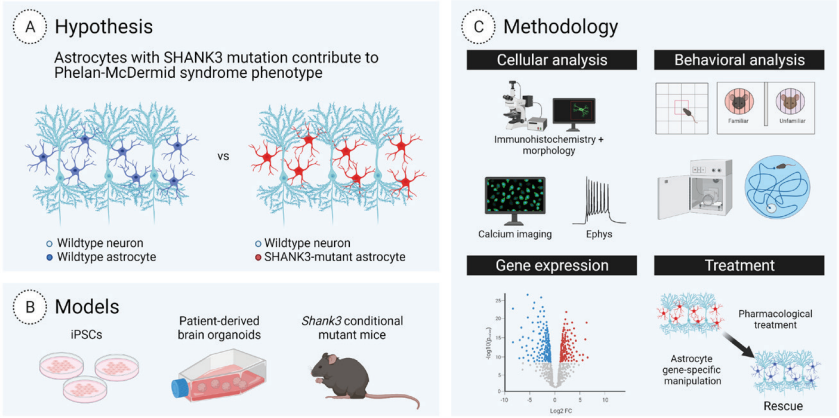
Davide Ragozzino, European Center for Brain Research, Santa Lucia Foundation, Rome, Italy

Tobias Boeckers, Institute of Anatomy and Cell Biology, Ulm University, Ulm, Germany

Matthew Holt, Center for Brain and Disease Research, VIB-KU Leuven, Leuven, Belgium

Mutations in the SHANK3 gene are one of the most common diagnosed causes for autism. However, we still know surprisingly little about the consequences arising from mutations in this gene. Since their original discovery, SHANK3 mutations have most commonly been studied in neurons. However, recent evidence suggests that astrocytes, a largely overlooked brain cell, may also play a key role in the development of autism. Astrocytes provide critical metabolic and trophic support to neurons and have recently been found as key players in the formation and maturation of neuronal circuits. Therefore, astrocyte dysfunction, resulting from SHANK3 mutation, may lead to problems in neuronal circuit formation and maturation, which will ultimately lead to behavioral and cognitive abnormalities.
Our consortium brings together several experts in the field of SHANK3 and astrocyte-biology, to tackle these questions using an array of innovative models that include genetically engineered mouse models, as well as human brain organoids capable of closely mimicking human cellular physiology.
Understanding which brain cells are key players in autism, and how SHANK3 mutations impact normal function during disease pathophysiology will allow us to discover and design successful therapies for neurodevelopmental disorders.



Daniel Hillier

UnscrAMBLY

Project Title: Understanding brain circuit dysfunction in amblyopia using large-scale multimodal recordings in a new visuomotor task applied to animal models and patients

Project Coordinator:

Daniel Hillier, Institute of Cognitive Neuroscience and Psychology, RCNS and Pazmany Peter Catholic University, Budapest, Hungary; Institute of Molecular and Clinical Ophthalmology Basel, Switzerland

Project Partners:

Maria-Magdolna Ercsey-Ravasz, Transylvanian Institute of Neuroscience and Babes-Bolyai University, Cluj-Napoca, Romania

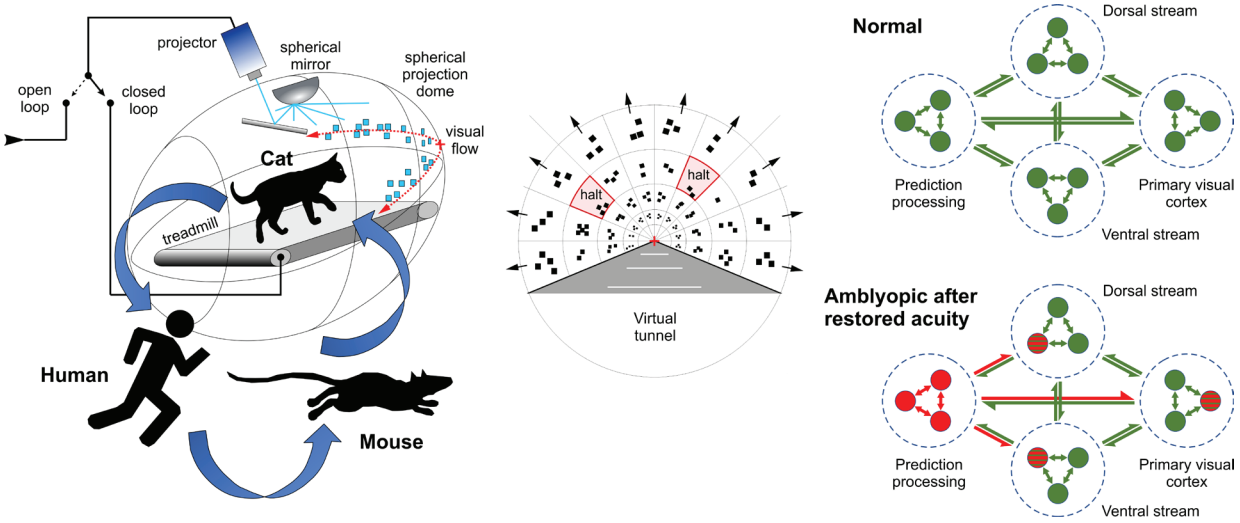
Alan Urban, Neuro-Electronics Research Flanders (NERF), VIB, Dept of Neuroscience KU Leuven, Leuven, Belgium

Koen Vervaeke, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

Zoltan Zsolt Nagy, Dept of Ophthalmology, Semmelweis University, Budapest, Hungary

Amblyopia (also known as "lazy eye") is one of the most studied neurodevelopmental vision disorders. Amblyopia must be diagnosed early and treated promptly because current treatments cannot efficiently recover lost vision beyond the age of 8 years. Only a small fraction of about 200 million affected patients, mostly those living in locations with high-quality healthcare and education structures in place, have access to timely and precise diagnosis and long-term support. The lack of proper treatment can lead to permanently decreased performance in everyday tasks including reading, driving or walking, motivating us to develop a new, efficient and widely accessible test for diagnosis and treatment monitoring. Our study aims to exploit the capacity of the brain to predict expected changes in the visual scene, especially those caused by our own motion. Subjects will pedal or run forward in a virtual reality corridor while brain activity, eye- and limb motion is recorded. We briefly halt the visual motion at small regions of the scene and analyze brain activity, eye- and limb-motion data. Using machine learning we determine differences between healthy and amblyopic subjects. In humans we use noninvasive recording that captures brain surface activity. Magnetic resonance imaging could also record deep brain activity but requires a fixed body and head for prolonged times thus is not applicable to our study. To collect high-resolution data also from deep regions of the brain we use cats and mice as amblyopia models. Visual function of the cat is very similar to humans. We use functional ultrasound imaging in behaving cats to link activity of deep brain areas

to amblyopia. Genetic tools available in mice allow us to test the functional role of brain regions involved in amblyopia in even more detail. This combined method will help us to provide a very robust network view of the origins of amblyopia and serve as a first step to set new and better directions for therapy. Our new method may be applicable to other neurodevelopmental disorders, providing a widely useful tool for clinical diagnosis and basic research.



Legend: A) Human, cat or mouse subject is moving forward in a virtual reality corridor. B) Brief perturbations (halts) of the coupling between self-generated visual flow and locomotion activate prediction error computations while large-scale activity is recorded in each species. This task may reveal the role of prediction computations in amblyopia. C) Functional networks of brain areas will be inferred from species-specific functional ultrasound imaging, 2P imaging, and hd-EEG.