

ERA-NET Neuron NEWSLETTER 23



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News From NEURON II

The kick-off meeting of NEURON Cofund will be held in Berlin, January 11-13, 2016. On the agenda: a workshop on: 'How to reinforce the interactions between scientists, clinicians and the society in the field of brain research?'

After a thorough peer-review process, 10 research projects of the "Neurodevelopmental disorders" JTC and 5 of the "ELSA (Ethical, Legal, and Social Aspects of Neuroscience)" JTC, were selected to be funded by the corresponding funding organizations.

From the desk of the coordinator | December 2015



Priv.-Doz. Dr.
Marlies Dörlöcher

Understanding the causes of brain diseases and finding the treatment for them is one of the great challenges of the 21st century that necessitate combined efforts by the scientific and clinical research communities involved in neurosciences. Expanding the understanding on current challenges and opportunities requires the involvement of additional stakeholders, among them patient organizations and the general lay public.

In this line, the activities of our new ERA-Net phase, NEURON Cofund, will start with a dialogue between brain researchers and patient organizations at a workshop entitled: 'How to reinforce the interactions between scientists, clinicians and the society in the field of brain research?' that will take place in Berlin on January 12th, 2016. Renowned representatives of European science and patient umbrella organizations will discuss means to improve collaboration.



More information can be found on our website
<http://www.neuron-eranet.eu/index.php>
era-net neuron

Produced by CSO-MOH, IL

A new Joint Transnational Call (JTC) for proposals in the area of traumatic injuries to the nervous system is planned for the beginning of 2016. The pre-announcement has been published on December 17, 2015 in NEURON's website: www.neuron-eranet.eu.

In 2015, NEURON partner organizations launched a joint call for proposals in the area of neurodevelopmental disorders. The aim of the call was to facilitate multinational, collaborative research projects to address important questions relating to the neurodevelopmental nature of neurological and psychiatric disorders. The proposals accepted for evaluation ranged from understanding basic mechanisms of disease to proof-of-concept clinical studies in humans. The international peer review panel offered its funding recommendations for the best research consortia, and 10 of them will be awarded more than 8 million euros by the corresponding partner organizations. The projects selected for funding cover a diversity of topics within the field of neurodevelopmental disorders from genetic causes of autism, epilepsy and cognitive impairment to visual disorders like amblyopia.



NEURON II NSC partners at the meeting in Helsinki, 2015

Another JTC launched by NEURON in 2015 was the "European Research Projects on Ethical, Legal, and Social Aspects (ELSA) of Neuroscience". The aim of the call was to facilitate multinational, collaborative research projects that will address important questions regarding ethical, philosophical, legal and socio-cultural aspects related to neuroscientific research and recent advances in the field. For this call, 5 research consortia will be funded with about 3 million euros, again following the recommendations of an international peer review panel.



Young scientists attending the poster session Helsinki 2015

In Mid-September, 2015, NEURON's Network Steering Committee (NSC) convened in Helsinki, Finland, for the concluding meeting to approve the funding recommendations of the two JTC and to discuss the coming steps of its next generation project: NEURON Cofund.



Scientists and NSC partners at the symposium Helsinki, 2015

Alongside with the NSC meeting, a Mid-Term symposium was held where the coordinators of the 12 funded projects of the 2013 JTC on "Mental Disorders" reported on their results as depicted in the abstracts below. Early-career scientists involved in these projects attended the symposium and presented their results in a well-attended posted session.

With this, I would like to wish all our friends and colleagues a peaceful and merry Christmas and Hannukah, and a happy and successful New Year.

Marlies Dorlöchter.



Claudia Buss

Biological mechanisms of transgenerational transmission of early life stress (MecTranGen)

Project Coordinator: Claudia Buss, Charité Universitätsmedizin Berlin, Berlin, Germany

Project Partners: Elisabeth Binder, Max-Planck Institute of Psychiatry, Munich, Germany

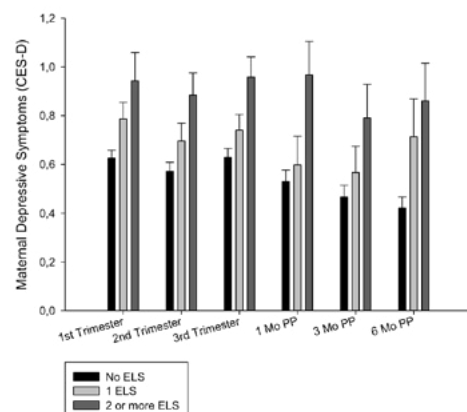
Katri Räikkönen, University of Helsinki, Helsinki, Finland, Michael Meaney, McGill

University, Montreal, Canada

Pathik Wadhwa University of California, Irvine, USA



MecTranGen addresses the problem of early life stress (ELS), like exposure to childhood sexual/physical/emotional abuse and neglect, and its mental and physical health consequences for the exposed individual as well as for the next generation. Growing evidence suggests that the consequences of exposure to abuse or neglect in childhood may be transmitted to a woman's offspring. Children of mothers exposed to ELS have a significantly higher risk of developing neurodevelopmental and psychiatric disorders. We do not adequately understand the pathways of the trans-generational transmission of ELS at this time. MecTranGen is comprised of studies critical for identifying targets for intervention(s), which can break the cycle of trans-generational transmission. Our preliminary data, after a little over 1 year into the project, support the expected hypotheses that women with ELS exhibit more depressive symptoms during pregnancy as well as postpartum (see Figure [PP: postpartum]). Higher maternal depression is associated with less sensitive parenting behavior, which is a risk factor for less optimal child neurodevelopment and for behavioral/mental health problems and neurocognitive impairments. Our preliminary results furthermore point to altered brain anatomy, as assessed with magnetic resonance imaging (MRI) in the newborn offspring of women exposed to ELS. These ELS-associated changes in the brain of offspring are independent of maternal depression and of parental behavior as evident from MRI scans performed shortly after birth showing that the brains of ELS-exposed offspring already follow a different developmental trajectory in utero than the brains of non ELS-exposed offspring. For the remaining duration of the project we will focus on ELS-associated alterations in stress biology during pregnancy, changes in maternal, placental and infant genes (i.e., epigenetic changes) and their association with maternal postpartum mental health, maternal parenting behavior and fetal and infant brain development. The understanding of these underlying biological pathways is critical for elucidating the cause of mental health problems in children of mothers exposed to ELS. It constitutes the first step in risk identification and in developing timely interventions, prior to the biological embedding of the adverse maternal experience in the child.





Froylan
Calderon de
Anda



The role of TAO2 in brain connectivity and Autism Spectrum Disorders (TAO2)

Project Coordinator: Froylan Calderon de Anda, ZMNH, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Project Partners: Claudia Bagni, VIB Center for the Biology of Disease/KULeuven Center for Human Genetics, Leuven, Belgium

Karun Singh, Stem Cell and Cancer Research Institute McMaster University, Hamilton, Ontario, Canada

Stephen Scherer, The Center for Applied Genomics, Hospital for Sick Children, Toronto, Ontario, Canada

Abstract

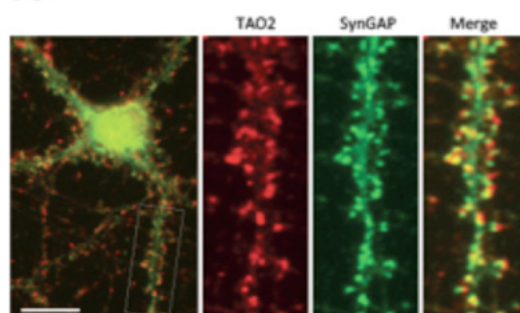
There is strong evidence that genetic mutations contribute to the risk for Autism spectrum disorders (ASDs). In the current grant we are studying the TAO2 gene due to the converging evidence linking it to ASDs, with the aim to better understand disease pathophysiology using multiple model systems.

We characterized TAO2 knockout (KO) mice, and found behavioral impairments (e.g. social deficits) and gross brain morphological defects similar to ASDs patients. Deeper investigation revealed that TAO2 is expressed in dendrites and spines, and TAO2 KO mice display significant defects in dendrite branching, spine and synapse formation, culminating in electrophysiological connectivity deficits.

TAO2 may also be involved in a monogenic form of ASDs (Fragile X syndrome, FXS), because it is a putative target of Fragile X mental retardation protein (FMRP). Excitingly, we found FMRP interacts with TAO2 mRNA and suppresses its translation at synapses, suggesting TAO2 plays a pathogenic role in FXS.

Finally, to determine if new mutations in TAO2 contribute to ASDs, initial exome and whole genome sequencing was performed and uncovered 3 previously unidentified de novo mutations (not present in parents), and 8 inherited missense variants that are not present in an unaffected sibling. Our initial characterization of one of the de novo mutation demonstrates it ablates TAO2 kinase activity, causing a striking impairment in neuronal morphology.

A



Taken together, our team's multiple lines of evidence strongly suggest that TAO2 is a new ASD candidate risk gene that warrants further investigation, and may lead to novel insight into ASD pathology.

Fig 1. TAO2 accumulates on spines of mature cultured neurons and localizes with postsynaptic marker SynGAP (A). Scale bar: 10 μ m



Véronique
Deroche-
Gamonet



Cocaine addiction: a translational study to identify and characterize dysfunctional neuronal networks in cocaine addiction (COCADDICT)

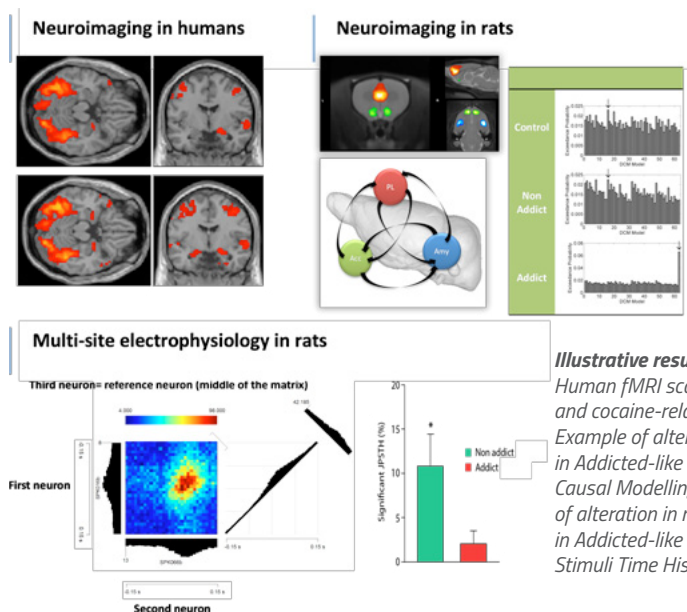
Project Coordinator: Véronique Deroche-Gamonet, Psychobiology of addiction, NeuroCentre Magendie, Inserm U862, University of Bordeaux, Bordeaux, France

Project Partners: Cyril Herry, Neuronal circuits of associative learning, NeuroCentre Magendie, Inserm U862, University of Bordeaux, Bordeaux, France

Marco Leyton, Department of Psychiatry, McGill University, Montreal, Canada

Rainer Spanagel, Institute of Psychopharmacology, Central Institute for Mental Health (CIMH), University of Heidelberg, Mannheim, Germany

Among the estimated 14 million cocaine users worldwide, addiction develops in about 15-20%. This differential susceptibility could reflect a specific reorganization of brain circuits in the vulnerable individuals. COCADDICT proposes a novel translational approach to identify these alterations, based on coordinated studies in human cocaine users and a high validity animal model and suggests that cocaine produces multiple changes in the brain, including addiction-related and unrelated alterations. To identify relevant changes, we compare, in humans and animals, cocaine users who have and have not lost control over their drug use. The project is multilevel: MRI brain imaging is used to measure large changes in the shape, activity, and communication between brain regions, in both humans and anesthetized rats. This work is complemented by electrophysiology to simultaneously measure the activity of individual cells within multiple brain regions in addicted-like rats seeking for cocaine. Finally, by using state-of-the-art brain activation techniques such as optogenetic, we can establish causal mechanisms. Taken together, we hope to identify and ultimately reverse the neurobiological signatures of cocaine addictive behavior.



Illustrative results of CocAddict. Top left: Human fMRI scans in response to neutral (top) and cocaine-related videos (bottom). Top right: Example of alteration in network connectivity in Addicted-like rats as revealed by Dynamic Causal Modelling analysis. Bottom: Example of alteration in neuronal circuit connectivity in Addicted-like rats as revealed by Joint Peri Stimuli Time Histogram analysis.



Kristina
Friedland



Hyperforin analogues, Zinc and TRPC6 channels – a new antidepressant concept? (HYPZITRP)

Project Coordinator: Kristina Friedland, Friedrich-Alexander-University
Erlangen / Nuremberg, Department of Chemistry and Pharmacy, Molecular & Clinical
Pharmacy, Erlangen, Germany

Project Partners: Alexandre Bouron, CNRS, Laboratoire de chimie et biologie des métaux,
Grenoble, France

Gabriel Nowak, Institute of Pharmacology / PAS, Krakow, Poland

The HypZiTrp consortium focusses on the role of Zinc and TRPC6 channels for the pathophysiology of depression. TRPC6 channels are regulators of synaptic plasticity, they are permeable for divalent cations including Zinc and are activated by the brain derived neurotrophic factor and Hyperforin, the major antidepressant component of St. John's wort. Interestingly, Hyperforin is a specific activator of canonical transient receptor potential-6 (TRPC6) and its antidepressive properties are mediated by activation of this nonselective cation channel. However, there are a few disadvantages in using Hyperforin as an antidepressant drug, among them its low stability and its ability to induce Cytochrome P450 3A4 (CYP3A4) that may lead to interactions with other drugs. As Hyperforin is an acylated phloroglucinol derivative we hypothesized that the essential pharmacophore could be derived from its phloroglucinol moiety. The first mono- and diacylated phloroglucinol compounds were tested for their Hyperforin-like activity profile and it turned out that the active ones were also specific for TRPC6 but did not induce CYP3A4. However, no increase in affinity was observed. Therefore, during the first year of our project more derivatives were synthesized and investigated for their structure-activity-relationships. It was shown that for the activation of TRPC6, two acyl side chains are necessary but their symmetry is of no importance. However, it seems that there is only a modest increase in activity going along with the lipophilicity of the compounds. As a next step, selected compounds will be investigated regarding their selectivity for TRPC6 channels as well as their antidepressant effects in animal models of depression.



Iiris Hovatta



Novel molecular pathways and biomarkers of anxiety disorders (AnxBio)

Project Coordinator: Iiris Hovatta, University of Helsinki, Helsinki, Finland

Project Partners: Christoph Turck, Max Planck Institute for Psychiatry, Munich, Germany

Angelika Erhardt, Max Planck Institute for Psychiatry, Munich, Germany

Alon Chen, Weizmann Institute of Science, Rehovot, Israel

Anxiety disorders are common mental diseases affected by both genetic and environmental factors. To investigate the molecular mechanisms involved in the pathogenesis of stress-induced anxiety, we have investigated a mouse model of psychosocial stress in two genetic backgrounds, the C57BL/6 and DBA/2 mouse strains. These strains respond to stress with distinct coping mechanisms, 61% of the C57BL/6 and 20% of the DBA/2 mice being resilient to stress. We have identified 433 genes that are differentially expressed due to chronic stress in the bed nucleus of stria terminalis, a key brain region in the regulation of anxiety. We are currently carrying out proteomics analysis from the same model, allowing us to integrate results from the transcriptomic and proteomic analyses. In parallel, we have investigated epigenetic differences in the blood cells of panic disorder patients and healthy individuals and have identified ten DNA methylation differences. Intriguingly, some of these are located within the same genes that show evidence for association in our genome-wide association study of panic disorder. In the next phase of the study, we will perform a converging analysis of mouse and human results and form specific hypotheses that will be addressed in functional studies in mice. This approach could lead to the establishment of biomarkers to more accurately diagnose anxiety disorders and to the identification of molecular targets towards the development of more effective treatments.

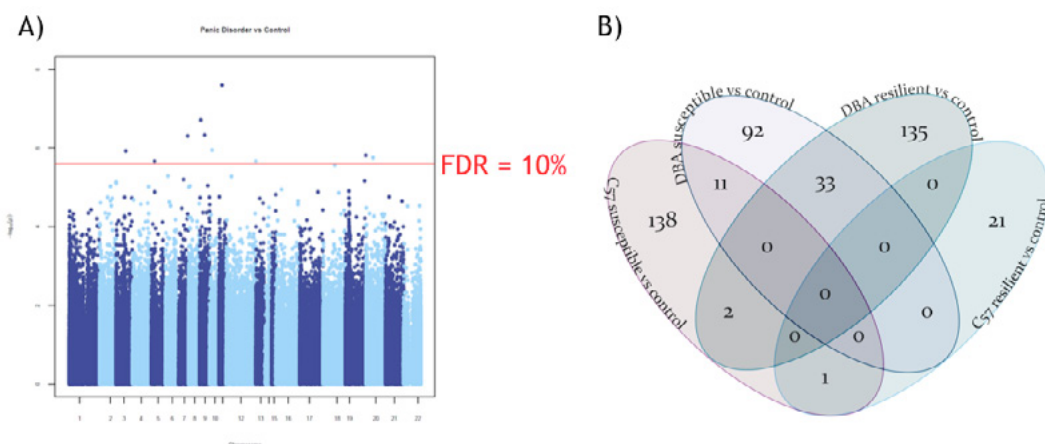


Figure 1. Genetic findings of the AnxBio consortium. **A)** Results from an epigenome-wide association analysis carried out in 132 panic disorder patients and 195 controls. DNA from blood cells was analyzed on the Illumina 450K methylation array. Each dot represents a single CpG site. Ten CpG sites were hypermethylated in panic disorder patients compared to controls with the false discovery rate (FDR) of 10%. **B)** We subjected C57BL/6 (C57) and DBA/2 (DBA) mice to chronic social defeat and divided the stressed animals into susceptible and resilient groups based on their behavior in the social preference test carried out after social defeat. We subsequently collected their bed nucleus of stria terminalis tissue and carried out RNA sequencing. The figure shows the number of differentially expressed genes with fold change > 1.3 and p < 0.01.



Vera
Kalscheuer



Molecular Mechanisms of Brain Function in mTOR-Deficient Intellectual Disability Syndromes (mTOR-DIDS)

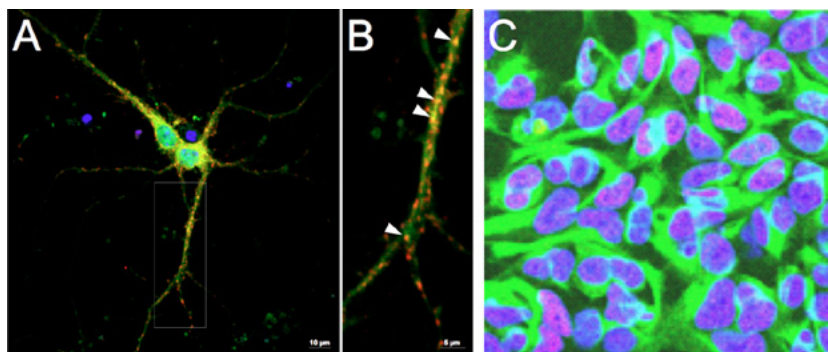
Project Coordinator: Vera Kalscheuer, Max Planck Institute for Molecular Genetics, Research Group Development and Disease, Berlin, Germany

Project Partners: Vania Broccoli, Ospedale San Raffaele s.r.l., Division of Neuroscience, Milan, Italy

Susann Schweiger, Institut für Humangenetik, Universitätsmedizin-Mainz, Germany

Rainer Schneider, Institute of Biochemistry and Center for Biomolecular Sciences, Innsbruck, Austria

The international mTOR-DIDS consortium studies the pathophysiology of three genetic syndromes characterized by intellectual disability (ID) of various degrees: Rett syndrome (RTT), atypical Rett syndrome (CDKL5 disorder) and Opitz/BBB/G syndrome (OS). Individuals with RTT and CDKL5 disorder manifest overlapping clinical features, including severe motor, cognitive, and behavioral abnormalities. OS causes several abnormalities along the midline of the body and about 50% of the patients have mild ID and developmental delay. We and others have linked these syndromes to hypoactivation of the mammalian target of rapamycin (mTOR) signaling pathway, a pivotal cellular cascade that plays an important role in several protein-synthesis dependent forms of learning and memory. However, the underlying mechanisms of the detected deficiency are far from being understood. A better understanding is a prerequisite for the identification of therapeutic targets for interventional strategies for these and other related disorders. In the first year, the consortium made important progress in establishing the prerequisites for further investigations of disease-relevant changes at different levels: biochemical, cellular, at the synapse and in the relevant mouse models. For example, we could show that Cdkl5 interacts with its newly identified complex partner implicated in mTOR signaling in vivo and that in cultured mouse neurons they co-localize in distinct puncta along dendrites (Fig. 1A, B). Furthermore, we have established neural progenitor cells from patients with OS (Fig. 1C). These will be differentiated into neurons, which will be used as one of the model systems to further investigate the influence of the disease-associated mutations on hypoactivation of mTOR.



(A) Cdkl5 (red) and one of its newly identified binding partner (green) partially co-localize (yellow) in primary mouse neurons. **(B)** Higher magnification of the inset shown in A. **(C)** Neural progenitor cells from a patient with OS.



Hannes Lohi

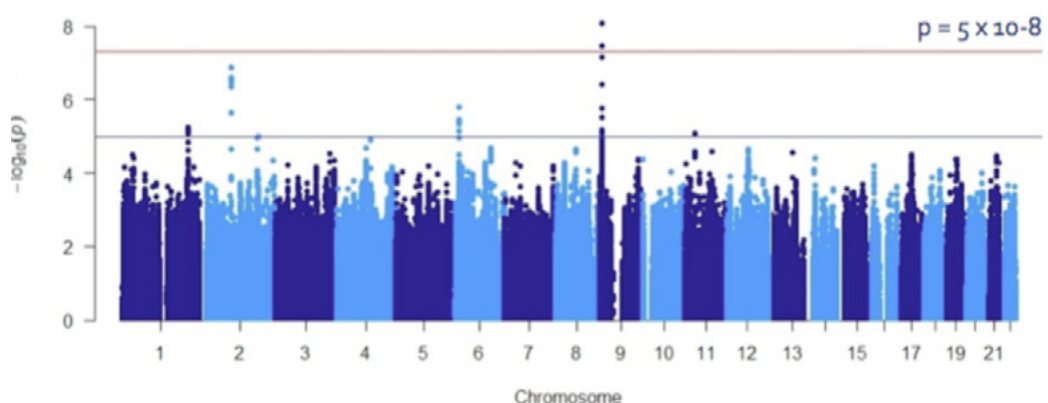


Discovering genetic risk variants for neuropsychiatric disorders and their consequences using dogs, humans and mice (CBGC)

Project Coordinator: Hannes Lohi, Research Programs Unit, University of Helsinki, Finland
Molecular Neurology

Project Partners: Paul Arnold, Mathison Centre for Mental Health Research and Education, University of Calgary, Calgary, Canada
Rui Costa' Champalimaud Center for the Unknown, Champalimaud Foundation, Lisbon, Portugal

Children with psychiatric disorders such as obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) suffer from highly disabling symptoms that interfere with their ability to function in day-to-day life. These conditions have strong genetic susceptibility but few risk genes have been discovered to date. Our group, the Comparative Behavioural Genomics Consortium (CBGC) has taken an innovative approach of studying OCD- and ADHD-related traits across humans, dogs and mice to gain novel insights about how genetic variants lead to childhood psychiatric disorders, and ultimately to identify new avenues for early identification and treatment of these devastating conditions. We have established significant study cohorts with proper phenotyping approaches across anxiety traits in both dogs and human and continue expanding them. Genome wide association studies in both species have discovered several new genomic loci with neuronal candidate genes across anxiety traits. We will compare the discoveries between species to investigate possible shared biological etiologies between human and dog. We have also initiated functional and behavioural characterization of the candidate genes in knockout mouse models using advanced endoscopic and optogenetic approaches to investigate the role of the genes in neuronal circuits that may predispose to these detrimental anxieties.



Total # of SNPs: ~5,162,437

Figure 1. Genome wide association study of a population sample of ~17 000 children and adolescents (6-18 years) with a quantitative measurement of obsessive compulsive traits identified a novel OCD gene. The function and role of this gene in neuronal circuit and behavior is being studied in a mouse model with advanced optogenetic approaches. The association of the gene in canine compulsion is also being investigated.



Luc Mallet



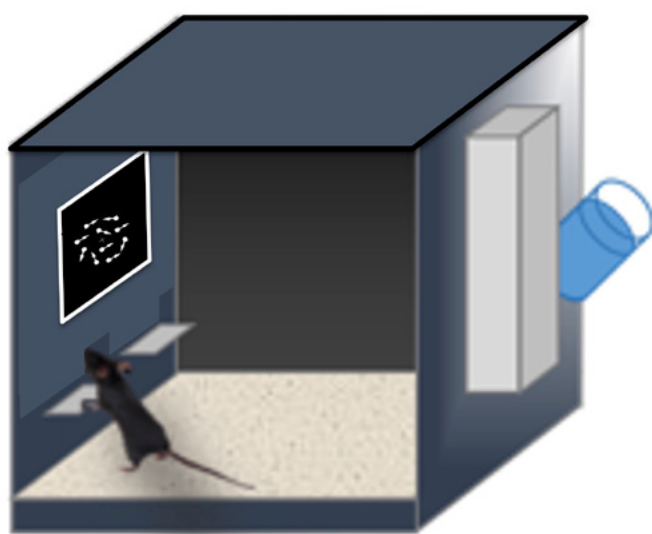
Uncertainty monitoring vs. inhibition of action in obsessive-compulsive disorder: role of the subthalamic nucleus and effects of stimulation in humans and rodents (TYMON)

Project Coordinator: Luc Mallet, ICM (Institut du Cerveau et de la Moelle épinière), Paris, France, and Personalized Neurology & Psychiatry University Department, Hôpitaux Universitaires Henri Mondor – Albert Chenevier, Créteil, France

Project Partners: Lars WOJTECKI, Center for Movement Disorders and Neuromodulation, Department of Neurology and Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine-University, Düsseldorf, Germany

Rui COSTA, Champalimaud Center for the Unknown, Lisbon, Portugal

Our project is focused on the understanding of the compulsive behaviors in OCD, which can be seen as a combination of two mechanisms: a) Uncertainty-monitoring: a deficit in accumulating sensory evidence would trigger repetitive checking behavior as an attempt to reduce uncertainty before making a choice, and b) Inhibitory control of action: failing to put an end to a sequence of checking actions triggered by contextual cues would result in repetitive checking. We designed a perceptual decision-making task using randomly moving dots in which we manipulate the uncertainty level by changing the degree of global motion coherence within the cloud of moving dots. The task design will be implemented to explore the electrophysiological correlates of checking in patients. In parallel, we aim at implementing a similar decision making task in mice. Because of the challenge it represents for mice to acquire the procedure, a high throughput behavioral system has been setup



and a dedicated software has been programmed to automatize the training procedure. For both humans and mice, this task will probe uncertainty in action selection, but not in action performance. To explore action monitoring and control, we are developing a translational novel task assessing confidence about an already-accomplished action.



Salah El
Mestikawy



VGLUT3 and vulnerability to addiction (COCACE)

Project Coordinator: Salah El Mestikawy, Douglas Institut universitaire en santé mentale, Département de Psychiatrie, McGill University, Montréal, Canada

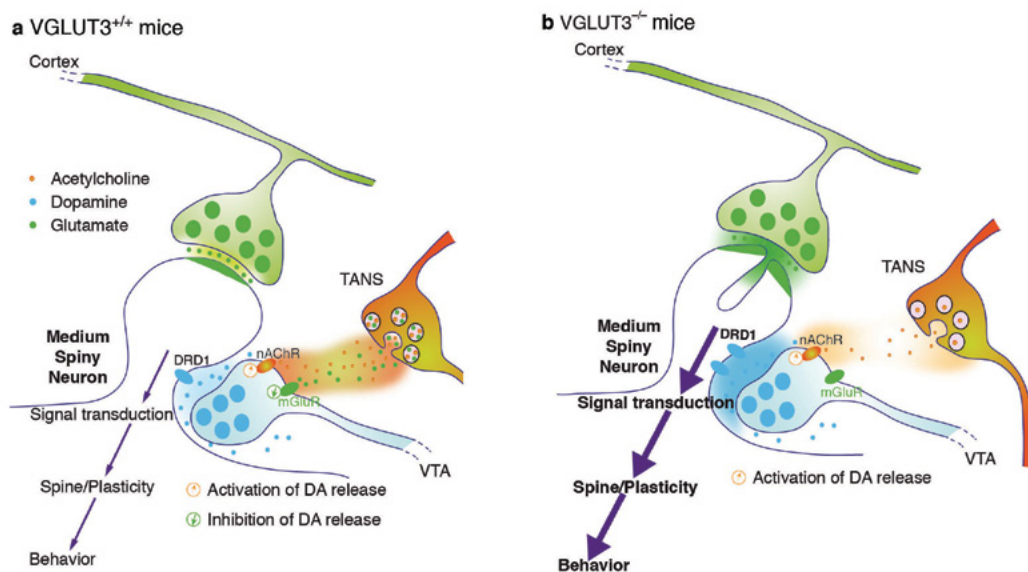
Project Partners: Frank Bellivier, Service Universitaire de Psychiatrie, GH St-Louis Lariboisière F Widal, Paris, France, Stéphane Jamain, INSERM U 955, IMRB, Psychiatrie Génétique, Hôpital Henri Mondor, Créteil, France

Christian Rosenmund, Neurocure NWFZ, Charite Universitaetsmedizin, Berlin, Germany

Åsa Mackenzie, Dept of Organismal Biology, Uppsala, Sweden

Addiction is a compulsive behavior that takes place at the expense of most other activities and destroys many lives. The secret of addiction lies in the dysfunction of brain communications in the reward system. To communicate with each other, neurons use one specific chemical messenger called neurotransmitter. We made the surprising discovery that a small population of neurons in the reward center uses two transmitters. The goal of our project is to investigate the implications of this neuronal "bilingualism" on addiction. In our project we combine approaches on mouse and human neurons..

During the first 18 months of the COCACE project we identified a gene and a neuronal mechanism that increased the vulnerability of mice to cocaine. In addition, we analyzed the gene responsible for this neuronal bilingualism and found that its rate of mutation was 10 times higher in human suffering from very severe addiction. In other word, we have identified a vulnerability marker of addiction in mice and humans. Our findings could lead to the establishment of alternative medications for the treatment of addiction. During the next 18 months, we will continue to investigate the molecular mechanism underlying these discoveries and to screen for human with mutations of this marker.





Martin
Schaefer



Role of inflammation and related processes in the development, phenomenology and treatment of depression (INFLAME-D)

Project Coordinator: Martin Schaefer, Kliniken Essen-Mitte, Essen, Germany

Project Partners: Lucile Capuron, Université Bordeaux, Bordeaux, France,
Annamaria Cattaneo, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
Astrid Friebe, Ruhr University Bochum, Bochum, Germany, Marion Leboyer, Mondor
Institute for Biomedical Research, Paris-Est-Créteil, France

Major depression is one of the most important reasons for years lived with disability. However, the knowledge on the pathophysiology of depression is limited. The INFLAME-D project investigates the role of inflammation in the phenomenology and treatment responsiveness of depression in vulnerable populations. Four different tasks have been developed to investigate risk and resiliency factors for IFN- α -induced depression and influence of antidepressant (pre-) treatment on immunological factors (task 1), behavioral/ molecular changes underlying the IFN- α treatment in mice (task 2), the role of inflammatory processes in the development, management and evolution of idiopathic unipolar and bipolar depressive disorders (task 3) and the role of metabolic alterations in inflammation and its subsequent mood effects in laboratory rodents (task 4). In a kick-off meeting and following skype conferences interdisciplinary cooperation has been discussed in detail regarding animal models, immunological, genetic and clinical investigations. The protocol for the clinical trial (task 3) was developed together and first patients have been recruited in Germany. In addition blood-samples from the different patient collectives in task 1 are collected and prepared for specific immunological and genetic measurements at the different labs of the partners in Italy and Germany. So far Task 1 has already developed significant preliminary results in term of biological factors underlying IFN- α induced depression. Animal models in task 2 are under investigation.



Julia C. Stingl



Role of genetic polymorphisms in drug metabolizing cytochrome P450 enzymes expressed in the brain for affective disorders (BrainCYP)

Project Coordinator: Julia C. Stingl, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany

Project Partners: Roberto Viviani, Department of Psychiatry and Psychotherapy III, University of Ulm, Ulm, Germany

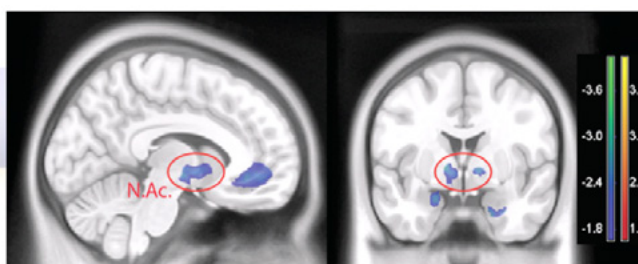
Magnus Ingelman-Sundberg, Department of Psychiatry and Pharmacology, Section of Pharmacogenetics, Karolinska Institutet, Stockholm, Sweden

Rachel F. Tyndale, Department of Pharmacology, Toronto, Ontario, Canada

The drug metabolizing enzymes CYP2D6 and CYP2C19 are known to metabolize several classes of psychoactive drugs. Genetic polymorphisms in the CYP2D6 and CYP2C19 genes alter the level of the corresponding enzymatic capacity and are also associated with various brain phenotypes. Transgenic mice expressing human CYP2D6 and CYP2C19 genes show pronounced behavioral phenotypes and biochemical alterations in the brain. In this research project we combine animal, preclinical, behavioral and clinical methods in order to obtain a mechanistic insight into the role of the cytochrome P450 enzyme polymorphisms in brain-related phenotypes such as affective symptoms like anhedonia or cognitive dysfunction. The first results (Sweden) showed that mice carrying the human CYP2C19 enzyme are more sensitive to chronic stress and show more despair-like behavior than wildtype mice. This state can be ameliorated with common antidepressant drugs like citalopram.

For CYP2D6 (Canada), the animal studies pointed to a lower level of anxiety in transgenic mice carrying the human CYP2D6. In a model assessing brain CYP2D6 activity and in the liver, CYP2D6 induction by codeine was shown in the brain while not observed in the liver.

For the studies in humans (Germany), functional paradigms assessing different axes of the negative valence and positive valence/approach motivation process domains have been established to assess brain function in anxious and depressed psychopathological phenotypes. We will now test healthy individuals who will be genotyped for CYP2D6, CYP2C19 and other drug metabolizing for these brain imaging paradigms.



Functional imaging of positive valence/approach motivation: choosing between delicious snacks activates the nucleus accumbens, a centre associated with motivation in animal studies (red circle), and ventral medial prefrontal areas associated with valuation.



Christine
Winter



Development of feed-back-controlled neuromodulation strategies for the treatment of intractable repetitive hyperkinetic movement disorders (RD_aDBS)

Project Coordinator: Christine Winter, Technische Universität Dresden, Germany

Project Partners: Konstantinos Meletis, Karolinska Institutet, Stockholm, Sweden

Alberto Priori, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan, Italy

Traditional drug treatments for psychiatric diseases are often associated with poor symptom alleviation, treatment resistance and side-effects. We believe that this in part is due to lack of both spatial (where in the brain) and temporal (when in connection with symptom manifestation and presentation) specificity of drugs. Amongst those conditions requiring better basic understanding and improved treatment is Tourette syndrome. Tourette syndrome, once considered rare, is in fact relatively common as it afflicts approximately 1% of the population worldwide. To better understand the causes of Tourette syndrome we first studied the behavioral and electrical phenomena arising in animals with specific brain abnormalities associated with Tourette syndrome. Based on clinical evidence, we generated a transgenic rat that overexpresses the dopamine transporter. These rats exhibit increased grooming and oral stereotypy upon environmental stressors and drug challenges. The behavioral responses and their sensitivity to clonidine but not fluoxetine indicate that the repetitive symptoms of the transgenic rats resemble those found in Tourette syndrome and are distinctive from other repetitive symptoms as found in obsessive compulsive disorders. Neurobiologically, we associate overexpression of the dopamine transporter to alterations in the dopamine system as well as in specific network activity patterns and brain site volumes all found in Tourette syndrome patients. In a first translational approach, we see analogies in electrical brain signals associated with repetitive symptoms in transgenic rats and tics in Tourette syndrome patients. With these findings we envisage the creation of a device that targets the implicated brain areas only at the time-point when stimulation is needed. In this way we believe we can provide improved symptom relief for Tourette syndrome patients and improve their quality of life.