ERA-NET Neuron

NEWSLETTER 29

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News From NEURON Cofund

NEURON 2018 Call for Proposals for Transnational Research Projects on Mental Disorders is closed. 124 preproposals were submitted, involving 533 research groups

JTC 2017 on "Synaptic Dysfunction in Disorders of the Central Nervous System" - 12 projects were chosen for funding out of 93 pre-proposals. Total grant volume for the 12 projects: 12.4 m€

From the desk of the coordinator | June 2018

Marlies Dorlöchter

The year 2018 started with the successful launch of NEURON's eleventh Joint Transnational Call. The call topic is "Mental Disorders". Mental health and mental disorders are being addressed by a NEURON call now for the third time. In this call, research questions of the entire lifespan are encouraged with a focus on young patients since many mental disorders develop during childhood, adolescence and early adulthood. An extraordinary high number of proposal submissions shows that we address a continuously urgent demand in this field of research.

The Call Secretariat for JTC 2018 "Mental Disorders" is hosted by the Spanish NEURON partner MINECO. In a two-step review process the most promising proposals will be selected for funding. Moreover, NEURON continued its quest for improving scientific quality and reproducibility in neuroscience. Invited experts and NEURON partners came together

Funded by the European Commission

More information can be found on our website
http://www.neuron-eranet.eu/index.php
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Produced by CSO-MOH, IL

in symposium on "Open Science" in Tel Aviv, Israel, to explore how open access publication and data sharing can boost the impact of research. To this end, we invited renowned international speakers to tackle the issue from both the researchers' and the funders' perspective. All participants readily agreed that transparency in science is a vital feature for achieving higher data quality and reproducibility of research results.

Open access publication is one means to promote transparency by making the access to research results easier. We are grateful that the invited researchers openly shared their views on this issue with us. They pointed out that, on the one hand, the benefit of open access publication is evident. It enables data-driven replication and that it may spark new research. Moreover, open access to data helps using synergies and prevents unnecessary duplication, thus enhancing efficient use of resources. On the other hand, the researchers also identified hurdles that prevent scientists from publishing in open access. Issues range from the difficulty for researchers to assess the quality of open access journals to the question of intellectual property rights. These constraints deserve serious consideration.

This symposium was the first step to identify NEURON's path to promote Open Science. NEURON will continue to intensely discuss this important issue for our future funding policy.

Sincerely yours,

Marlies Dorlöchter.

Workshop on "Open Science", January 2018 | Tel Aviv

The NEURON workshop on open science in January 2018 in Tel Aviv focused on open access to research including publication and data management plan policies. Open Access is the practice of providing online access to scientific information (publications and data) that is free of charge to the end-user. Motivation: Scientists and citizens should be provided with uncomplicated access to (publicly funded) research results.

Read more about the Tel Aviv workshop at http://www.neuron-eranet.eu/en/808.php

David Mellor

Reducing bias and improving science with preregistration

David Mellor

Project Manager, Incentive Programs, Center for Open Science, Virginia, **USA**

The combination of a strong bias toward statistically significant findings and flexibility in data analysis results in irreproducible research. The Center for Open Science (https://cos.io) is a non-profit culture change and technology organization whose mission is to increase the integrity of scientific research. To achieve that mission, we investigate barriers to reproducibility, advocate for improvements to scientific process through data sharing and reducing bias in data analysis, and build tools to enable the actions for which we advocate. Preregistration is an important action in this process, whereby data collection and analytical plans are specified in advance. This helps make the distinction between exploratory (hypothesis generating research) and confirmatory (hypothesis testing) more clear (Nosek et al., 2018; http://www.pnas.org/content/early/2018/03/08/1708274114). Both are important. But currently, researchers are rewarded for presenting the results of exploratory work using confirmatory tools. This makes research findings more publishable, but at expense of their credibility. Funders and journals can support preregistration by requiring researchers to pre-specify their data collection procedures (e.g on the OSF https://osf.io/prereg) or by encouraging the use of Registered Reports (https://cos.io/rr) in which research designs are submitted for in-principle acceptance at a journal prior to realizing the results of the work. This reduces bias in publication and improves study design earlier in the research lifecycle.

Find this presentation at: https://osf.io/gsf7w/

Christine Winter

Open access – the science perspective

Christine Winter

Laboratory Head Experimental Psychiatry, Dept. of Psychiatry, Charité, **Germany**

Obviously, open access to data and publications benefits not only science in general but also ethical science in particular. Despite this agreement, it is practiced only moderately by academic researchers.

Why does the scientist often enough decide against it? Is it the predictable and ratable attractiveness of traditional journals guaranteed by a rigorous peer review process and the power of established trademarks as till date the journal’s quality is what people will be assessed by, or is it the uncertainty with new payment regulations and the not knowing whether these new concepts and journals will last? Alternatively, is it a vague feeling of a responsibility to restrict and protect sensitive information supported by the comfort of restriction? Maybe it is the ‘John Bohannon’ and the ‘Dr. Fraud’ experiments that feed the skepticism?

With respect to making own data accessible it in fact may also be that till date, data is considered a standalone research output that in the current system loses its exclusive power once shared without exploitation. At this workshop we discussed these motivational factors and strategies to overcome them from a personal, a scientific and an institutional view.

Idan Menashe

Open access – the public health science perspective

The Good, the Bad and the Ugly of open access science

Idan Menashe

Negev Autism Center, Department of Public Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, **Israel**

The emergence of open access journals in the beginning of the 21st century has reformed the way scientists publish and access to scientific data. This revolution in scientific publication improves the visibility of scientific papers to a broader audience, and thus helps reducing the gap between wealthy and poor institutions.

However, open access publication has some unfavorable aspects. One example is the emergence of ‘predator’ journals, which exploit the pressure in the academia to publish papers to charge publication fee from authors without providing them with adequate editorial services. Thus, cautious should be taken when reading or publishing papers in open access journals. In my talk, I discussed additional Good, Bad and Ugly aspects of open access science, as well as the potential involvement of social media tools in future science.

Anton Bespalov

Assessing quality of research practice: From manuscript checklists to auditing

Anton Bespalov

Managing Partner, Partnership for Assessment and Accreditation of Scientific Practice PAASP, Heidelberg, **Germany**

There is a variety of measures being discussed and implemented in order to stimulate open science culture and to improve quality of research data. Of particular relevance for basic science where publications are still the only well-established currency that supports various aspects of decision making (from funding to hiring), journals started to introduce publication checklists. For example, Nature Publishing Group has been using a checklist developed specifically for its journals dealing with manuscript submissions in life sciences.

Four years after these checklists were introduced, their impact has been analyzed by Malcolm Macleod and the NPQIP Collaborative group who revealed a substantial improvement in the reporting of risks of bias in in vivo research in NPG journals to a level that has not been previously observed. While these changes are certainly encouraging, one needs to be aware of the “danger of normative responses, whereby scientists simply satisfy the guidelines or checklists at a time when it is too late to take corrective actions on experimental conduct (Vogt et al (2016) PLoS Biol 14(12): e2000598).”

Indeed, as presented and discussed during the Workshop, there is indeed a clear evidence for such “normative responses”. Such situation is not surprising because there is currently no connection between desired behaviors (such as transparent reporting) and reinforcement (such as publications in higher IF journals). As a result, we may well observe other behaviors (other than those that are desired) unintentionally reinforced.

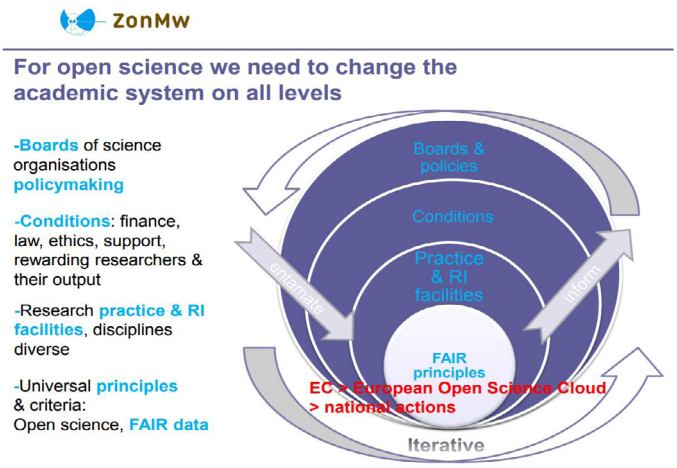
Why funding organizations (should) wish to promote openness and sharing of research data - a European perspective

Margreet Bloemers

Margreet Bloemers

Programme manager, ZonMW, **The Netherlands**

Research funding agencies have a special interest in data sharing, since it contributes to the output of research and accelerating innovation in research and society. Data management is a key condition for data sharing. Data sharing is an integral part of the transition to open science which takes place in the international academic community. This transition is only possible when all academic stakeholders participate: research funders and performing organisations, researchers, research infrastructures (service providers and facilities), policy makers, and professionals in practice. Moreover, this transition must take place at all levels of the academic system (see figure). ZonMw, the health research funder in the Netherlands, is active in this transition.



Research data management is a complex task and requires specific expertise and a positive attitude towards data sharing and open science. Introducing data management in research projects is a challenge, particularly in international research programming, as research communities and countries differ in their readiness, culture, attitude, legislation, available finances, infrastructure and expertise for this part of the research process. Countries may raise obstacles that are related to all levels of the academic system as the figure shows. When introducing research data management and setting requirements for data sharing NEURON must be prepared to take actions at all of these levels. In case the full implementation of research data management is still a bridge too far, a lot can be done in promoting awareness among researchers, show casing, and guiding researchers to (e.g.) services and facilities for standardisation and data repositories which are best fit for NEURON’s field of work.

Openness and reproducibility: a funder’s perspective

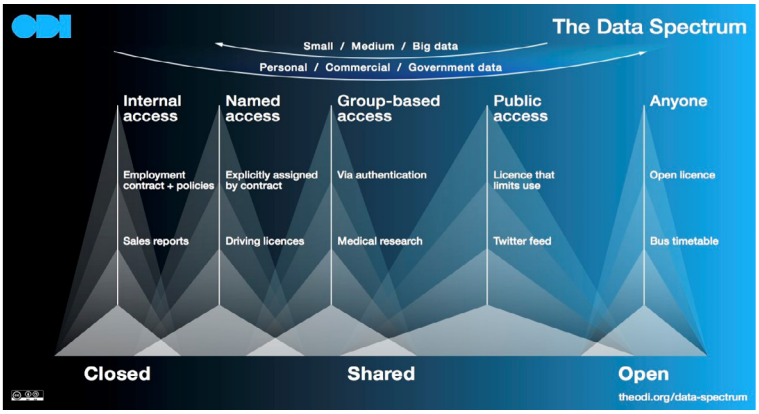
Geraldine Clement-Stoneham

Geraldine Clement-Stoneham, Head of Knowledge Management and Scholarly Communication, Medical Research Council, a part of UK Research and Innovation, **United Kingdom**

Funders play an essential role in promoting the principles of open research data and their policies can support openness, clarity and reproducibility of the research methods and findings. Sharing data also helps maximising the value of the data collected, and enables new discoveries. The Medical Research Council (MRC) requires a data management plan (DMP) to be submitted which each grant application. The DMP gives researchers the opportunity to describe the data they will re-use or generate; how they will manage and curate data effectively throughout its lifecycle, as well as how data will be shared. The peer review process then establishes if the approach is commensurate to the proposed research project.

The MRC Open Access (OA) policy specifies that each article must include a statement on how underlying research materials, including data, can be accessed. In addition, it requires all peer-reviewed research papers published in journals or conference proceedings to be made freely available on Europe PubMedCentral within six months of the first on line publication.

In the context of clinical trials, public health interventions and observational studies, the MRC also has articulated additional expectations. Studies should be registered with the ISRCTN registry. The results of the study (whether negative of positive) should be published without unnecessary delays after the end of a study. The study protocol, analysis plan and all relevant statistical analyses should be made available publicly before the start of a study.



The MRC also recognises that preprints are a valuable way for researchers to publish their results. Preprints can help disseminate research findings early on, and offer a publishing avenue for results which might not be suitable for the more traditional research paper format. Researchers are actively encouraged to share their pre-peer reviewed manuscripts via established preprint servers, and they can cite preprints in their MRC funding applications.

https://mrc.ukri.org/research/policies-and-guidance-for-researchers/

http://europepmc.org/

Sascha Helduser

NEURON measures

Sascha Helduser, Programme manager, DLR-PT, **Germany**

NEURON set out to address scientific, societal, and regulatory challenges in the field of neuroscience. In this respect, NEURON strives to promote high level research and quality standards. It is widely accepted that Open Access and data sharing are important elements that help to improve quality and reliability of research results. The benefits include that it enables data-driven replication and that it may spark new research. Moreover, open access helps using synergies and prevents unnecessary duplication, thus enhancing efficient use of resources. Another aspect, that makes Open Access and data sharing an important topic for NEURON is that publicly funded research results should be publicly accessible. NEURON’s Scientific Research Agenda, that sets the roadmap for NEURON’S future activity, even recommends that an “Open access data policy should be a prerequisite for funding in the NEURON framework”. Implementation of measures promoting Open Access within NEURON’s framework requires a common understanding and the alignment of national / regional regulations. Hence, the NEURON partners organized a dedicated workshop to discuss what measures can be implemented NEURON’s funding scheme and which next steps NEURON can take.

Open Science Workshop

January 24th, 2018
Tel Aviv, Israel

NEURON Joint Call 2017: "Synaptic Dysfunction in Disorders of the Central Nervous System"

12 transnational research consortia are under negotiation to be funded under the umbrella of the NEURON JTC 2017 'Synaptic Dysfunction'. In total, 59 research groups from 15 European countries, Canada and Israel collaborate in these projects. The total funding volume of the call amounts to about 12.4 M€. Here you can learn about the projects and their goals. We wish them all much success!

Mechanisms of neuropsychiatric genetic diseases of the SNARE complex: towards therapeutic intervention [SNAREopathy]

Ruud Toonen

Project Coordinator:
Ruud Toonen, Vrije Universiteit (VU) Amsterdam, The Netherlands

Project Partners:

Federico Zara, Istituto Giannina Gaslini, Genova, Italy

Holger Lerche, Eberhard-Karls University of Tübingen (EKUT), Germany

Christian Freund, Institute for Chemistry and Biochemistry, Berlin, Germany

Camila Esguerra, UiO Centre for Molecular Medicine Norway, Norway

Epilepsy is a severe and disabling disease affecting about 1% of the world's population. Despite years of intense research about 30% of all epilepsies cannot be treated by available drugs. This poses a substantial economic burden for the EU health systems and individuals and their families. To develop new and better treatment options, a detailed knowledge of the mechanisms leading to epilepsy is urgently required. In this proposal, we will focus on a group of difficult-to-treat, severe epilepsies that is caused by gene mutations which mediate the communication between nerve cells (the so-called synaptic transmission). This communication is essential for a regular function of the brain, and mutations disturb the fine balance between nerve excitation and inhibition which can lead to epileptic seizures. Our consortium unites experts in the genetics of epilepsy and neurobiologists working on synaptic transmission to identify the exact mechanisms leading to epilepsy using several sophisticated mouse and zebrafish models, as well as human cell models which are derived from skin biopsies that will be transformed into human neurons in culture. Based on the identified epileptic mechanisms, we will select some of the models for drug screening in neuronal cells and zebrafish to search for novel medications to better and more specifically treat the severely affected epilepsy patients.

Amygdala synaptic neuromodulatory mechanisms and role of mGlu4 receptor in Autism Spectrum Disorders [MAGNOLIA]

Cyril Goudet

Project Coordinator:

Cyril Goudet, Department of Neuroscience, Univ. Montpellier, France

Project Partners:

Ingrid Ehrlich, University of Tuebingen, Germany

Julie Le Merrer, Université de Tours, France

Amadeu Llebaria, Institute of Advanced Chemistry of Catalonia, Spain

Autism spectrum disorders (ASD) refers to a range of developmental disorders of the brain. Affected persons show repetitive stereotyped behaviors and are challenged in their social abilities, emotional states and in how they perceive things in the world. Drug treatments for ASD are currently very limited, and those available are poor at improving social abilities, so there is a need to identify new drugs that would help alleviate these symptoms.

Therefore, a more complete understanding of the underlying mechanisms of ADS in the brain is indispensible. As for many neurodevelopmental disorders, there is evidence for a dysfunction of synapses, the communication points between neurons. Their activity can be controlled my modulatory receptors, among them the glutamate receptor type 4 (mGlu4) which could be an intervention point for several brain-related diseases. Indeed, we recently demonstrated that facilitating the activity of mGlu4 receptor relieves autistic-like behavior in mouse models of ASD. The purpose of this research project is to further explore the therapeutic potential of mGlu4 receptor. We will focus on a brain region called the amygdala and its connections with other brain structures that together form a network regulating social, cognitive, emotional and sensory behavior.

Our hypothesis is that mGlu4 receptor controls the function of specific aspects of this network, which is dysfunctional in ASD but can be rescued when mGlu4 receptor is activated by drugs. We will test this hypothesis using two mouse models that show ASD-like deficits and working with an interdisciplinary team of researchers which are experts in animal behavior, synaptic communication and development of new classes of light-sensitive drugs that can switch mGlu4 receptor on and off by light. The latter is of particular importance as it allows for the precise investigation of the role of mGlu4 receptor in space and time. Findings from our project will expand our knowledge about the molecular, synaptic and network mechanisms in the brain that underlie ASD and the beneficial effects of mGlu4 activation on autistic symptoms, and hopefully pave the way for the development of new classes of drugs that can provide more effectively treatment.

Imaging synaptic plasticity in therapeutic sleep deprivation for major depression [SleepLess]

David Elmenhorst

Project Coordinator:

David Elmenhorst, Institute of Neuroscience and Medicine Molecular Organization of the Brain, Germany

Project Partners:

Jeroen Verhaeghe, University of Antwerp, Belgium

Pedro Rosa Neto, McGill University, Canada

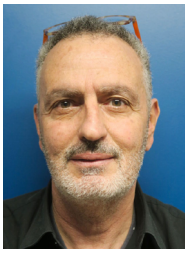
Staying awake for a night improves the mood for a lot of patients with depression very quickly. Unfortunately this beneficial effect often only lasts until the next sleep period. There are only a few other options in depression that show such a fast anti-depressive action. If the main players in this mechanism could be clarified, it is likely that this information could be used for novel treatments options or optimizations. A recent model of depression proposes that the connection between neurons (synapse) is strengthened during sleep deprivation which restores a deficit in the depressive brain.

A novel brain imaging technique (Positron Emission Tomography (PET) imaging of the synaptic vesicle protein 2A (SV2A)) allows to monitor the amount of synapses in the living brain of humans and animals which suffer from depression.

A major problem in investigating animals inside a scanner is that they usually have to be immobilized, which is usually done by anesthesia. Since both anesthesia and sleep are subject to hamper with the parameter of interest, a stress free PET imaging method for awake animals will be developed.

We are convinced that synaptic density determined with PET has the power to become an indicator for the success of therapeutic sleep deprivation and thus providing means for future stratifications of different therapies in major depression. Identifying and understanding the mechanisms that mediate the effects of sleep restriction is necessary to develop effective interventions. This project will test a model that can be used to improve schedule design.

VGLUT3 rare mutant and vulnerability to addiction [ADIKHUMICE]



Salah El Mestikawy

Project Coordinator: Salah El Mestikawy, McGill University, Canada

Project Partners:

Stéphane Jamain, Faculté de Médecine, Créteil, France

Florence Vorspan, Université Paris Descartes, France

Rafael Maldonado, Universitat Pompeu Fabra, Barcelona, Spain

Christian Rosenmund, Charite Universitaetsmedizin Berlin, Germany

Addiction is a compulsive pattern of drug-seeking/drug-taking behavior that takes place at the expense of most other activities. It leads to a loss of control despite negative consequences and reoccurring episodes of abstinence and relapse. Millions of people are affected by addiction to alcohol, drugs, gambling or sex. The economic costs for our society is tremendous. Despite this socio-economical burden we critically lack effective treatment. To make progress in the treatment of this devastating pathology we urgently need an in-depth understanding of the cellular and molecular mechanism underlying addiction. The key to understand and treat addiction lies in understanding the brain reward system.

As in the entire brain, neurons from the reward system use a combination of electrical and chemical signals to communicate with each other. These chemical messengers are called neurotransmitters. The neurotransmitters: dopamine, acetylcholine and glutamate are key players in addiction. Until recently, it was believed that neurons use only one neurotransmitter to signal. We made the surprising discovery that a small population of neurons from the reward system can use 2 transmitters (namely glutamate and acetylcholine) to communicate with other neurons, suggesting that they are functionally bilingual. Furthermore, we have recently shown that perturbation of these bilingual neurons dramatically increases vulnerability to addiction. The aim of our study is to extend these preliminary results in order to better understand the neuronal mechanisms underlying addiction. This study could lead to the establishment of alternative medications for the treatment of addiction.

Microglial control of synaptic function in stress response and vulnerability to depression [MicroSynDep]

Marie-Eve Tremblay

Project Coordinator: Marie-Eve Tremblay, Université Laval, Canada

Project Partners:

Igor Branchi, Center for Behavioral Sciences, Rome, Italy

Martin Fuhrmann, German Center for Neurodegenerative Diseases, Bonn, Germany

Bozena Kaminska, Nencki Institute, Warsaw, Poland

Maciej Lalowski, University of Helsinki, Finland

Valeria Mondelli, King's College, London, United Kingdom

Major depressive disorder (MDD) is one of the most relevant public health challenges at the clinical, social, and economic levels, costing over 120 billion euros in Europe alone. Alteration in the synapses, which are the structures responsible for communication among the principal brain cells, i.e. the neurons, has been hypothesized to underlie the onset of MDD. However, the mechanisms through which synaptic dysfunction contributes to this psychopathology are only scarcely known.

Microglia, which are immune cells of the brain, play a key role in regulating synaptic function and neuronal activities in the healthy and diseased brain. We therefore hypothesize that microglia are critically involved in the brain changes underlying both the onset of and the remission from MDD. Consequently, treatments able to modulate microglial function hold the promise of providing novel and more effective therapeutic strategies to treat this psychopathology.

The MicroSynDep consortium aims at exploring such hypothesis. To this goal, the consortium brings together a multidisciplinary partnership of European- and Canadian-leading experts, including clinicians and basic scientists, and will combine, in a translational perspective that is from preclinical work to clinical applications, studies on human brain and depressed patients with basic neurobiolgical research in animal models. We will employ a wide range of cutting-edge technologies to unravel the impairment of microglia-synapse interaction in MDD. Ultimately, the MicroSynDep project will lead to develop and implement in the clinics innovative treatment options for depression.

Targeting aberrant KAinate Receptors in Temporal Lobe Epilepsy [KARTLE]

Christophe Mulle

Project Coordinator: Christophe Mulle, University of Bordeaux, France

Project Partners:

Valérie Crépel, Aix-Marseille Université, France

Dirk Grimm, University of Heidelberg, Germany

Bernard Pirotte, Université de Liège, Belgium

In humans, the predominant form of Epilepsy - a chronic brain disease whose hallmarks are disturbed activity of nerve cells and recurrent seizures - is called temporal lobe Epilepsy or TLE. Unfortunately, forty percent of all TLE patients do not respond well to the current generation of pharmaceutical drugs, thus creating an urgent need for novel therapeutic and clinically relevant approaches.

Here, we aim to fill in this critical gap, by expanding on our data that a certain type of cell surface molecules (aberrant synaptic kainate receptors, KARs) markedly contribute to epileptiform activity in TLE patients within a specific region of the brain (dentate gyrus [DG], located in the hippocampus area). The central goal of our project is therefore to design and validate two parallel strategies to target aberrant synaptic KARs, in order to inhibit their activity and thereby alleviate the disease symptoms in TLE patients. In the first strategy, we will devise and characterize new pharmacological agents that selectively target and block aberrant synaptic KARs, and will then study their anti-epileptic activity in mouse models of TLE.

In the second strategy, we will exploit a cellular mechanism of gene silencing called RNA interference (RNAi) to achieve the same goal, i.e., to remove aberrant syanptic KARs. To efficiently and specifically deliver the molecules inducing anti-KAR RNAi to DG cells, we will engineer gene transfer vehicles based on non-pathogenic Adeno-associated viruses (AAV). Identical to the first strategy, these new AAV/RNAi vectors will then also be tested for anti-KAR activity in mouse models of TLE.

Finally, we will additionally validate the best candidates from both strategies in hippocampal tissues that were surgically extracted from TLE patients. As a whole, our project will extend pre-clinical studies in cells and animals to pathophysiologically most relevant human epileptic tissue, which should pave the way for future clinical translation of our innovative approaches.

A functional dissection of human nicotinic receptor polymorphisms linked to addiction and Schizophrenia [iPS&BRAIN]

Uwe Maskos

Project Coordinator: Uwe Maskos, Institut Pasteur, France

Project Partners:

Huib Mansvelder, VU University Amsterdam, The Netherlands

Petra Scholze, Medizinische Universität Wien, Austria

Smoking is the single most important cause of mortality worldwide. It is an addiction to nicotine that acts in the brain on nicotinic receptors, called nicotinic acetylcholine receptors (nAChRs). Human genetic studies have found alterations in the genome that increase the risk for smoking. These are found in several genes coding for nAChR proteins.

Additionally, human genetic studies have also highlighted a link between schizophrenia and alterations in nAChR genes. Schizophrenia hits about 1% of the population, and is a very debilitating, chronic relapsing disorder, that will not allow most patients to pursue productive professional lives. On top, smoking levels are very high, more than 80% of patients are heavy smokers, and so it is also important to study the link between schizophrenia and smoking.

We are proposing here a substantial project that analyses the function and the alterations in nicotinic receptors in human neurons in culture, and after transplantation into the mouse brain. This will be completed by recordings from human brain tissue obtained through surgery. Finally, transgenic rodents will be used to study the consequences when these genetic alterations are present.

This project will set the stage for renewed interest by pharmaceutical companies in developing medication targeting specifically the genetic alterations in the patients, in an approach referred to as "precision medicine".

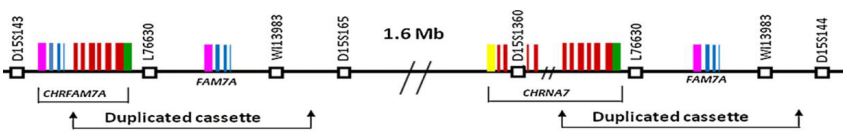
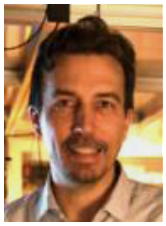


Figure 1. A map of the human CHRNA7 gene locus, demonstrating the human-specific CHRFAM7A duplication.

Multi-scale investigation of synaptic dysfunction after stroke [MISST]

Project Coordinator: Valentin U. Nägerl, Université de Bordeaux, France



Valentin U. Nägerl

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Jérôme Badaut, Université Bordeaux, France

Leszek Kaczmarek, Nencki Institute of Experimental Biology, Poland

Javier Defelipe, Universidad Politecnica de Madrid/ Instituto Cajal (CSIC), Spain

Baiba Jansone, University of Latvia, Latvia

Each year about 15 million people suffer a stroke worldwide, a disorder typically caused by lack of blood supply to the brain. Many patients survive a stroke acutely but are struck with life-long disabilities like paralysis, loss of speech, depression, loss of memory, and eventually dementia resembling Alzheimer's disease. While many lives were saved in recent years due to improved emergency and hospital care for acute stroke, therapeutic options for the chronic consequences of stroke are still missing. The main reason for this unfortunate situation is that we still do not know how the brain reacts to a stroke in the long-term and how these changes are linked to long-term disabilities which usually affect patients for their entire remaining life. The current application brings together the best and most experienced European researchers specialized in synapses, the structures responsible for communication between neurons, and experts in experimental stroke research. This unique consortium of excellence aims to investigate how a stroke in one brain region may affect the function of the whole brain and how these remote and chronic changes after stroke may be manipulated in such a manner that neurological dysfunction may be reduced or even partially or fully restored. Hence, the ultimate aim of the current consortium is to determine the underlying causes of chronic stroke and to pave the way for the development of effective cures.

In order to achieve this goal, the current group of European scientists will use novel animal models of chronic stroke and investigate tissue from stroke patients with highly innovative imaging technologies such as super-resolution microscopy and high-resolution whole brain and single neuron 3D reconstruction. First, we aim to characterize and understand the degeneration of synapses in brain areas far away from the injury induced by stroke in mice and man. Finally, we aim to use this knowledge to evaluate novel therapeutic concepts for the restoration of synaptic function thereby developing novel treatments for chronic stroke.

Linking synaptic dysfunction to disease mechanisms in schizophrenia - a multi-level investigation [SYNSCHIZ]

Project Coordinator: Ole Andreassen, University of Oslo, Norway

Project Partners:

Marcella Rietschel, Central Institute of Mental Health, Germany

Stefan Borgwardt , University of Basel, Switzerland

Marja-Leena Linne, Tampere University of Technology, Finland

Dirk Schubert, Radboud University Medical Center, The Netherlands

Magdalena Budisteanu, Alex Obregia Clinical Hospital of Psychiatry, Romania

Ole Andreassen

Schizophrenia is a severely debilitating mental illness characterized by hallucination, delusions, and cognitive disabilities and reduced functioning. It represents one of the major challenges for society, with large unmet patient needs and substantial health care costs to the European community. Over the past decade, it has become clear that schizophrenia is a disorder where different regions in the brain fail to communicate appropriately. In parallel, recent gene discoveries have pointed to dysfunctional communication of brain cells: the neurons. Together, these insights suggest that the connections between neurons in the brain - the synapses - are malfunctioning. However, the precise synaptic mechanisms leading to schizophrenia remain elusive.

The SYNSCHIZ project forms a collaboration of experts from Norway, Germany, Switzerland, Finland, Romania and the Netherlands to study synaptic dysfunction at various levels from genes to neuron cells to brain networks using state of the art methodology. This includes gene discoveries in large international samples, creating computer models of synapses, experimental validation of the models in neurons, and imaging of brain networks to test synapse function in humans. By investigating disease patterns related to synapse dysfunction at all levels from genes to brain networks we will elucidate the specific mechanisms in schizophrenia. Further, revealing these mechanisms can also lead to biomarkers – which can be used to predict the illness at an early stage, before the outbreak of severe symptoms. This will allow clinicians to reduce the duration of untreated illness and provide early support. SYNSCHIZ researchers are all experts in different fields. Together we can join the different pieces of the schizophrenia puzzle and target the ambitious aims.

Therefore, SYNSCHIZ will increase our understanding of the synaptic mechanisms behind schizophrenia and will stimulate new developments for treatment and potential prevention of mental illness. SYNSCHIZ is perfectly situated to transfer scientific discoveries into clinical applications.

Mapping and interrogating top-down control of the memory engram of the posttraumatic stress disorder [topdownPTSD]

Mazahir T. Hasan

Project Coordinator: Mazahir T. Hasan, Achucarro Basque Center for Neuroscience, Spain

Project Partners:

Stefano Puglisi Allegra, Fondazione Santa Lucia, Rome, Italy

Agnes Gruart, Pablo de Olavide University, Seville, Spain

Philipp Böhm-Sturm, Charité University Medicine, Berlin, Germany

Stephanie Le Hellard, University of Bergen, Norway

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Post-traumatic stress disorder (PTSD) is a psychiatric disorder of significant prevalence and morbidity, whose pathogenesis relies on paradoxical changes of emotional memory processing.

In PTSD, life threatening experience leaves a lasting trace of fear memory, which can last a lifetime. It is estimated that roughly 50% of the people world-wide will encounter a trauma-causing experience once in their lifetime. This generates a huge burden on the European Union citizens and calls for attention to tackle PTSD. There is no suitable treatment that is currently available to treat the cognitive features of PTSD, and/or to prevent its development.

The present project aims at investigating the neurobiological underpinnings (at a synaptic level) of acute and chronic response to a traumatic experience both in animal and human subjects, who will (susceptible) or will not (resilient) develop the chronic pathological phenotype. Understanding the neurobiological basis of PTSD can be of great help in the identification of innovative therapeutic strategies. This can be done through genetic, biomarker, imaging and psychological screening. By generating drugs that activate these molecular mediators of plasticity, it may be possible to enhance extinction of inappropriate fear associations.

Synaptic Dysfunction in Intellectual Disability Caused by SYNGAP1. Translational Research to Develop Human Models and Advance Pharmacological Treatments [TREAT-SNGAP]

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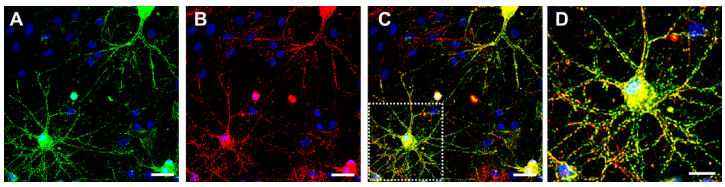
Àlex Bayés

Synapses allow communication between neurons and are also the site for storing sensorial information. It is for this reason that synapses are very important in learning and memory. Recent biomedical research has shown that synaptic dysfunction is at the centre of many brain disorders, especially in conditions where cognitive abilities are impaired, such as intellectual disability (ID) or autism spectrum disorders. The human SYNGAP1 gene encodes a protein that is highly enriched at brain synapses. Recent genetic studies have shown that mutations in SYNGAP1 cause ID. Actually, SYNGAP1 mutations could account for up to 1% of all ID cases, affecting thousands of people worldwide. Basic research studies using mice deficient for SYNGAP1 have shown that, indeed, a synaptic dysfunction is importantly contributing to ID. Nevertheless, there is still no efficient treatment for kids with this disorder. It is thus necessary that we understand in great level of detail the alterations occurring at the synapse if we want to develop SYNGAP1 deficiency treatments. Using mouse models we have studied proteomic alterations found at the synapse of SYNGAP1 deficient animals. This research has allowed us to propose four candidate drugs that we think might correct synaptic alterations, potentially improving this condition. Now we want to actively investigate the effect of these drugs in SYNGAP1 deficiency. As nowadays we have the capacity to develop neurons from human skin or blood cells, we will, for the first time, directly study human neurons obtained from SYNGAP1 patients. These human neurons will also be used to investigate the validity of mouse findings in a human research system. The ultimate goal of TREAT-SNGAP is to identify new strategies to treat ID caused by SYNGAP1.



Neurons derived from human induced pluripotent stem cells (iPSC) were labelled with the presynaptic marker Synaptophysin (panel A, green) and the postsynaptic marker PSD95 (panel B, red). Overlay of A and B images (in panel C) shows co-localization of, in yellow, of both presynaptic and postsynaptic markers, which is suggestive of the location of synapses. (D) Zoom in of framed region in C allows for better identification of yellow puncta, corresponding to individual synapses. The scale bars are 50 micrometers in panels A, B and C and 25 micrometers for panel D

Understanding psychosis, cognitive impairment and motor symptoms induced by NMDA receptor dysfunction: from mechanisms to prevention and therapy [NMDAR-PSY]

Dragos Inta

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Schizophrenia is one of the most severe psychiatric disorders with onset of symptoms mainly during young adulthood, followed in many cases by a lifelong chronic evolution that generates tremendous medical care and social problems. The origins of schizophrenia are so far unclear and most drugs used in the therapy of the disorders have been developed serendipitously.

A core symptom of schizophrenia is altered cognition, which cannot be improved by current medications. Interestingly, severe cognitive deficits, associated with sharp shrinkage of the hippocampus (a brain structure playing a key role in learning and memory), were found in patients with anti-NMDA receptor (NMDAR) encephalitis. This represents a recently discovered, mainly paraneoplastic form of autoimmune encephalitis, in which autoantibodies against glutamate NMDAR induce psychotic and often also motor symptoms (like severe catatonia) that are indistinguishable from those seen in schizophrenia. Whereas psychosis in these patients is largely curable, the lost long-lasting cognitive deficits cannot be efficiently treated.

In the present project, we aim to determine the possible beneficial effect of drugs enhancing NMDAR function to alleviate symptoms associated with NMDAR hypofunction both in genetically modified mice as well as in humans suffering from schizophrenia. Our approach is highly interdisciplinary including several morphological, electrophysiological, behavioral, as well as clinical and complex data analysis methods. By including two different cohorts of individuals with prodromal versus chronic, therapy-resistant schizophrenia, we aim to provide a differentiated view regarding the effect of NMDAR enhancers in specific phases of the disease.

Additionally, we aim to determine if the therapeutic response is influenced by genetic factors in these patients. Our project aims to bring together pre-clinical and clinical research: since pathological changes at molecular and cellular level cannot be studied in humans, we will analyze two genetically modified mouse lines with alterations in NMDAR in selective neuronal populations, and will extensively compare these data with those resulting from the analysis of humans suffering from schizophrenia or humans at high risk of developing the disease. The final goal of our study is to better understand the mechanisms by which NMDAR dysfunction induces the numerous, partly difficult to treat abnormalities seen in schizophrenia and anti-NMDAR encephalitis and to contribute to the development of more selective and efficient antipsychotic drugs.

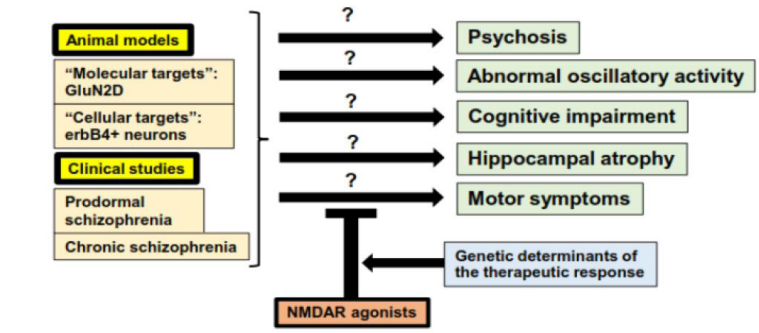

Fig.1. Schematic representation of the strategy NMDAR-PSY of the project. On one side, neurobiological mechanisms of psychosis-associated abnormalities and the possible beneficial effect of NMDAR agonists will be studied in genetically modified mouse models with NMDAR dysfunction restricted to erbB4-expressing cells (the receptor for neuregulin-1, main genetic risk factor for schizophrenia) or to the GluN2D subunit of the NMDAR. In parallel, using a similar multidisciplinary approach as in the animal models, neuroanatomical and functional correlates of psychosis will be investigated in individuals with prodromal ("Basel cohort") or chronic schizophrenia ("Jerusalem cohort") upon treatment with the NMDAR agonist D-serine. Additionally, it will be determined whether the therapeutic response to treatment with NMDAR modulators is influenced by genetic factors affecting glutamatergic neurotransmission in individuals with schizophrenia.

NEURON Joint Call 2017: "European Research Projects on Ethical, Legal, and Social Aspects (ELSA) of Neuroscience"

Three transnational research consortia are under negotiation to be funded under the umbrella of the NEURON JTC 2017 "Neuroethics (ELSA)". In total, 11 research groups from four European countries and Canada collaborate in these projects. The total funding volume of the call adds up to about 1.8 m€.

Addiction in the Brain: Ethically Sound Implementation in Governance [A-BRAIN]

Matilda Hellman

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Project Partners: Sarah Forberger, Leibniz Institute for Prevention Research and Epidemiology (BIPS), Germany

Patricia Conrod, Centre de Recherche, CHU Ste-Justine, Canada

Christian Hendershot, Centre for Addiction and Mental Health (CAMH), Canada

The project Addiction in the brain: Ethically Sound Implementation in Governance (A-BRAIN) studies the use and the implementation of neuroscientific research on addictions. The foundation of brain-based knowledge on addiction is the Brain Disease Model of Addiction (BDMA). This model explains and treats addictions by referring to the mechanisms in the brain. The model has, however, shown to neglect contextual and social factors and even the neuroscientific evidence itself is still far from being conclusive. Despite this, there are big hopes that the implementation of this model could revolutionize treating and handling addictions.

A-BRAIN studies the articulation and spread of the BDMA in different contexts: public media; scientific community, experts and policy-makers; prevention programs; and clients and staff in addiction treatment. Methods employed are surveys, group interviews and media content analysis. The international research consortium executing this project will develop guidelines for the implementation of neuroscientific research into the praxis of dealing with addictions in society. These guidelines take into account ethical considerations as well as the perspective of various groups concerned with addictions. The project will also develop and test a new instrument of measurement of attitudes towards the BDMA. The results also feed back into the neuroscientific research itself by communicating societal expectations and needs in the light of a sound implementation of neuroscientific research results.

The Future of the Body in the Light of Neurotechnology [FUTUREBODY]

Christopher Coenen

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Neurotechnology (NT) is mainly developed to restore or replace lost bodily functions (such as with cochlea implants) or to alleviate medical conditions (for example by means of deep brain stimulation). Since the 2000s, however, the idea became popular to use NTs not only to help people with impairments or diseases, but also to more generally enhance human performance and go beyond what is normally possible with the human body. Why should we not control a car, a computer or any other machine via brain-computer-interfaces (BCI) technology and use other NTs for boosting our performance? Would that not make us more efficient and more competitive?

In the project FUTUREBODY, we are going to investigate some of the chances and challenges raised by NTs in terms of their ethical significance and relevance to our societies, focusing on the human body and its envisioned merging with NT via the following means: technological modifications of the body in which technology replaces or augments bodily functions by means of surgical interventions (implants, prostheses), the use of technologies which modify the body without such interventions (non-invasive neurostimulation technologies), and the coupling of humans and artefacts via BCI technology.

We are going to look into philosophical aspects of NTs and societal expectations of what it means to be "normal", analyse some of the hard ethical problems in applying NTs, consider potential technical and social alternatives to these tools, and invite filmmakers, artists and designers to think creatively about where the use of NTs could lead us, as a society and as individuals. Since NTs are developed globally, FUTUREBODY is an international collaboration of researchers from Germany, Austria and Canada.

Therapeutic and Enhancement Uses of Neuroscientific Knowledge: A Question of Individual Autonomy? [THERENIA]

Juha Räikkä

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Knowledge produced by the neurosciences can be employed in treating neurological and psychiatric diseases and is also expected to enable the enhancement of human mental capacities even far beyond what is now seen as normal. While the former uses of neuroscientific knowledge are usually welcomed, the latter have faced extensive criticism, much of which relates to individual autonomy.

Given that the same neuroscientific techniques can be used in both therapeutics and enhancement, the attitudes towards the two ways of employing neuroscientific knowledge appear inconsistent with each other. Along with recent philosophical research, neuroscientific studies have also provided reason to question received conceptions of autonomy.

The main aim of this research project is to assess how individual autonomy is to be understood in light of the latest pertinent research and compare how, if at all, therapeutic and enhancement uses of neuroscientific knowledge differ from each other from the viewpoint of autonomy. The relationship between individual autonomy and other values – such as wellbeing, dignity, and justice – deemed pertinent to determining the moral and legal acceptability of using neuroscientific knowledge to modify human mental capacities will also be determined. In studying the questions, the project will employ both theoretical and empirical research methods.