ERA-NET Neuron

NEWSLETTER 22

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News From NEURON II

The European Commission approved the support the ERA-Net NEURON in the frame of the new Cofund instrument under Horizon2020 for additional five years. The Kick-off meeting will be held in Berlin, January 2016.

The final meeting of NEURON II will be held in Helsinki, Finland, in September 2015. It will also include the Mid-term symposium on "Mental Disorders", where PI's and young scientists involved in the funded projects will report on the progress of their research.

From the desk of the coordinator | July 2015

Priv.-Doz. Dr.
Marlies Dorlöchter

With highest pleasure we received recently news from Brussels that the European Commission will grant further support to the ERA-Net NEURON in the frame of the new Cofund instrument under Horizon2020. This means that our international network of funding organizations will continue working together for additional five years. We are eagerly looking forward to this new phase of NEURON in which we plan to tackle many issues of interest for the scientific community, such as the currently discussed topic of quality assurance and data reproducibility in science. New links to various other initiatives in the brain research area will be initiated and those already existing will be strengthened. As in the past, the Joint Transnational Calls for proposals will remain the core activity of NEURON Cofund.

The success of our proposal to the European Commission and the new work program were based on thorough and very creative discussions in several workshops. One of these

Funded by the European Commission

More information can be found on our website
http://www.neuron-eranet.eu/index.php
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was held in Malaga, organized by the Spanish NEURON member ISCIII. A summary of the workshop is depicted in this Newsletter.

NEURON traditionally coordinates scientific symposia on issues connected to the upcoming Joint Calls. A symposium on "External insults to the nervous system" was thus organized by NEURON's French members CNRS and INSERM on May 12, 2015, in Bucharest, Romania. A "Foreword" by the organizers and the abstracts of the presentations made during the symposium are provided here.

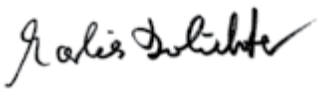
The concluding meeting of NEURON II will be held in Helsinki, Finland, in September 15-18, 2015. A part of this meeting will be dedicated to the Mid-term symposium on the projects funded under the frame of the Transnational Joint Call on Mental Disorders (www.neuron-eranet.eu/en/405.php).The Principal Investigators involved in the funded projects, who started their projects about a year ago, will present the progress of their work so far as well as the hurdles and road blocks they encountered.

Within NEURON's traditional support of scientists at their early career stages and the encouragement of networking among the PhD students and postdocs involved in the funded projects, we offer travel stipends to young scientists to the symposium in Helsinki, where they will present posters on their work.

With the meeting in Helsinki the funding organizations involved in our ERA-NET will step out of NEURON II and will enter NEURON Cofund at the kickoff meeting in Berlin, January 2016!

With this brief report I wish you all a pleasant summer break,

Marlies Dorlöchter.



NEURON workshop on the Development of a Sustainable Framework for Cooperation

Dr. Teresa Chavarría Giménez and Ana Tardon Ibañez from ISCIII, Spain, partner in NEURON II, organized a workshop on the "Development of a Sustainable Framework for Cooperation" in Malaga, Spain, on September 26, 2014. The workshop brought together 24 participants representing the 16 national research funding organizations participating in NEURON II.

The workshop focused on finding a common vision for a future sustainable cooperation grounds for a framework of funding research in the area of disease-related neurosciences, presenting better alignment of the National Research Funding Programmes in the frame of the Co-Fund scheme that was planned to be applied in Horizon 2020.

Dr. Daria Julkowska (Agence Nationale de la Recherche (ANR), France, and the Coordinator of the ERA-Net for Research Programmes on Rare Diseases, E-Rare), focused her presentation on the concept and activities of the new ERA-Net Cofund scheme as experienced by E-Rare: the forming of the consortia and the writing of the proposal and the financial plan.

The main points made were the compulsory implementation of one co-funded call per grant agreement with the possibility of implementation of additional activities, including the highly recommended additional joint calls. The EU contribution to funding of the co-funded call is proportional to the total funding budget commitments of the partners.

The budget commitment, the size and competitiveness in the field of the national research communities and the inclusion of countries with both strong community and less developed community, all these should be taken into account when planning the application of the ERA-Net Co-fund call budget.

It also should be important to encourage the motivation to fund as many research projects as possible in order to obtain the maximum EU contribution guaranteed in the Grant agreement

In his presentation, Mr. Mika Kallio (Project Manager/ WoodWisdom-Net Secretariat, Ministry of Agriculture and Forestry in Finland) summarized practical problems and solutions pertaining to the ERA-Net Plus scheme on issues related to EU top-up funding. He explained the implementation and management of a FP7 ERA-Net Plus as a funding model, where, similar to ERA-Net Cofund, the EC reimbursed 33% of the funding allocated by the partners for a Joint Transnational Call.

The financial requirements and responsibilities of the partners should be thoroughly discussed and cleared ahead, aiming to agree on a fair distribution of the major costs between the partners.

Participants attending the workshop in Malaga

From Left to right: Mika Kallio, Marlies Dorlöchter, Daria Julkowska and Marja-Liisa Niemi

The core of the presentation of Dr. Marja-Liisa Niemi's (Ministry of Education and Culture. Department for Higher Education and Science Policy, Finland; ESFRI Health and Food Strategic Working Group Delegate) was on the creation of synergies involving stakeholders while pointing to other EC-supported instruments besides the ERA-NETs: ERA-NET Plus, Article 169/185 networks, Article 185 action, self-sustaining networks, Joint Programming Initiatives (JPIs), all including 473 organizations from 52 countries.

In the development the funding instruments in the frame of the European Research Area, the main issues to be considered are:

- Addressing the grand challenges
- Providing access to expertise not available at home
- Enhancing development of competence of researchers and research managers
- Creating critical mass within research
- Enabling larger projects and integration along the whole innovation chain
- Helping to indicate and overcome barriers
- Adding visibility

In the discussion that followed the presentations, it was agreed that Era Net Cofund seems to be the best option for the set-up of the new NEURON programme. It should allow the funding of as many research projects as possible and the budget calculations and distribution should be made accordingly.

Cooperation with other initiatives, synergies should be pursued to build a better European research coordination, while improving the efficiency of the European Research Area resources to the benefit of European citizens.

NEURON symposium on External insults to the nervous system

Foreword

Etienne Hirsch

Bernard Poulain

Etienne Hirsch, Institut Neurosciences, Sciences cognitives, Neurologie, Psychiatrie de l'INSERM, PARIS, France and **Bernard Poulain** Institut des Sciences Biologiques, Centre National de la Recherche Scientifique (CNRS), Paris, France

A symposium on "External Insults to the Nervous System" was organized by ERA-NET NEURON II in Bucharest, Romania, on May 12, 2015. The symposium was attended by both researchers and students, including local young neuroscientists and clinicians.

The symposium main aim was to provide an overview on the research on external brain aggression and stimulate ideas on activities that NEURON II partners may jointly initiate to rapidly advance this field.

The broad scope of the symposium covered various sources of external aggression to the brain and nervous system, such as environmental factors, pathogens, and traumatic brain injury. These brain aggressions, although acute in nature, can result in neuronal cell death or the alteration in brain function, leading to chronic, long-term functional impairment for the patients, even for their whole life. Since in contrast to other organs, degenerated neural cells cannot be replaced or regenerate, the symptomatic manifestations of the neuronal damage persist for years. Therefore, development of restorative strategies and tools (e.g. brain-machine interfaces) to compensate for these handicaps are required.

Young scientists at the Symposium in Bucharest

The presentations in the first part of the symposium focused on epidemiological studies on brain aggression and infections to identify potential causes of brain diseases.

The second part of the symposium was dedicated to the role of drug abuse, stress and urbanization on the development of psychiatric disorders.

The symposium was concluded by two lectures on means to rectify brain insults by rehabilitation, exoskeleton and brain machine interface.

Altogether, this symposium enabled a discussion the mechanisms of brain injury caused by external aggression, the understanding of which will allow developing new modes of therapy for the devastating outcome of external insults to the nervous system.

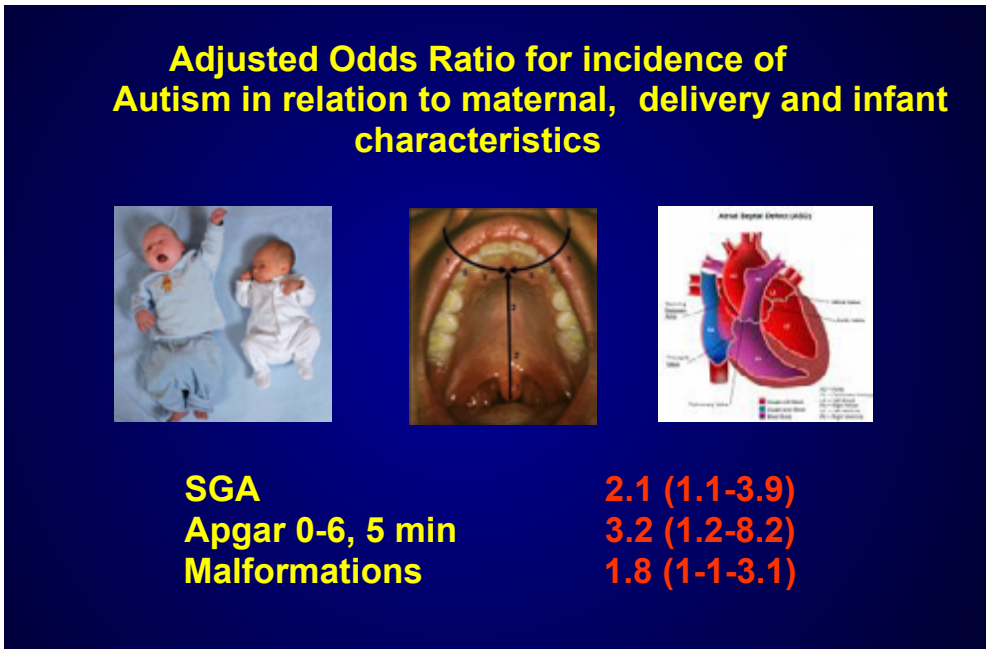
Christina M Hultman

Epidemiological Studies on Environmental Brain Aggression

Christina M Hultman, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

There is a general agreement that prenatal insults to the developing brain are associated with psychiatric and psychological disorders. Early risk factors to these disorders may be related to hypoxic-ischemic compromise to brain development, to genetic aberrations, to parental life style (diet, smoking, drugs) or traits (advanced parental age). The risk for schizophrenia, bipolar disorder, autism, anorexia and ADHD is two-fold higher in cases of adverse conditions during pre- and perinatal period. Low birth weight, fetal growth delay and asphyxia seem to be independent risks that may cause brain damage. However, we have shown in sibling-design studies that some early risk factors, like smoking during pregnancy, are not causal, but related to shared family traits. Advanced parental age, especially over 40 years, are related to a two-to-three fold increase in several child and adult psychiatric outcomes, compared to children of parents in their mid-twenties. Infections, violence and trauma in childhood and adolescence may also cause permanent damage to the brain. Another important risk factor is stress sensitization as it has been shown that childhood maltreatment increases the risk associated with adult trauma exposure. Structural abnormalities in the brain (corpus callosum) have been demonstrated among traumatized children.

An important challenge of neuroscientific research is to better distinguish between genetic vulnerability and environmental factors on as a source of long-term effects of brain development and if they mirror a true causal association. There is also a controversy on



how subclinical symptoms and signs should be measured and on the means to find biomarkers at an early stage. These controversies should be explored on large scale epidemiological studies using newly developed methods.

While due to higher standard of living, prenatal period is becoming safer and the possibilities to give children optimal conditions for their normal upbringing are rising, we need to extend our knowledge on which early signs and trauma persist, how the brain can be protected, how the recovery process can be facilitated and how suitable can animal models be to test these questions.

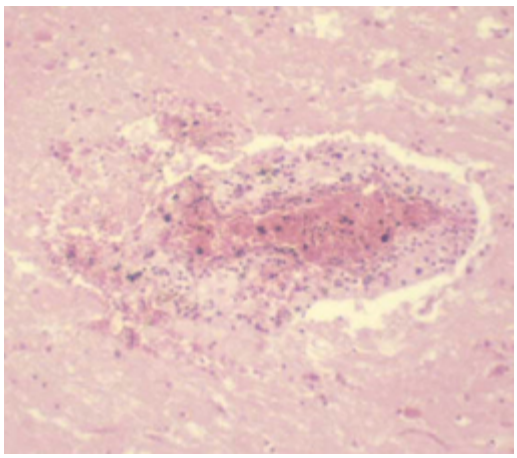
Additional, carefully devised epidemiological studies on early external influences to the brain (non-optimal birth conditions, asphyxia, infections, physical and psychological trauma, diet) should be designed. These studies, controlled for genetic influence, could employ sibling designs and multigenerational perspectives, cross-disorder studies and longitudinal studies. We also need to support the identification and treatment of modifiable risk factors and biomarker studies as well as new means of data collection.

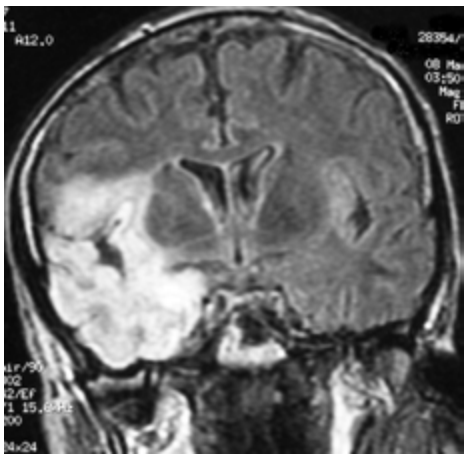
Tom Solomon

Nervous System Infections

Tom Solomon, Institute of Infection and Global Health, University of Liverpool, Liverpool, UK

Infections comprise some of the most important external insults to the nervous system. Although a range of pathogens can infect different compartments of the nervous system, encephalitis (inflammation of the brain parenchyma), caused by viruses, is especially important because of its devastating outcome. Whilst some viruses, such as herpes simplex virus, cause sporadic disease across the globe, others, such as Japanese encephalitis virus, are important emerging pathogens





resulting in geographically wide-spreading outbreaks. Even using the best available diagnostic tests, the aetiology of encephalitis is identified in only 30-50% of cases, pointing to the urgent need for new diagnostic approaches.

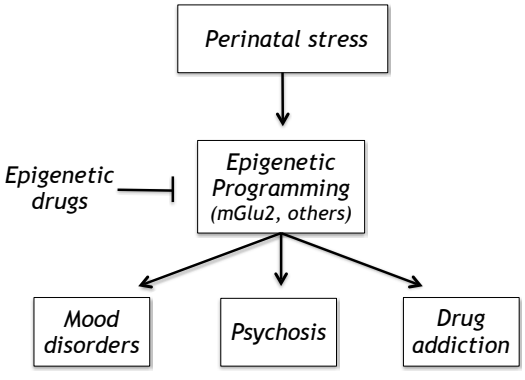
The mechanism by which pathogens cross the blood brain barrier is poorly understood, yet this might provide key insights into the pathogenesis of brain damage. Although antiviral treatments are available for some diseases, the outcome of these is often still poor. Better understanding is required on how viruses cause neuronal damage and how much "bystander" cell death of non-infected cells occurs during the infection. This damage is thought to be due to a poorly regulated inflammatory response, which may thus be amenable to ancillary treatments. Research on neurological infections provides one of the most promising opportunities for transnational neuroscience progress with translational impact.

Ferdinando Nicoletti

An epigenetic path to the treatment of the comorbility between depression, psychosis, and drug addiction

Ferdinando Nicoletti, LIA (International Associated Laboratory, University of Lille1, France; University Sapienza of Rome, Italy; IRCCS Neuromed, Italy.

Early life events contribute to the pathophysiology of all major psychiatric disorders, including depression, schizophrenia, and drug addiction. The development of a "pathological" epigenetic programming in response to early life stress may explain why these disorders are often associated and interdependent. Therefore, drugs that prevent or reverse stress-induced epigenetic programming may provide a new effective strategy in the treatment of psychiatric disorders, particularly in patients who are refractory to conventional medication. Rodents exposed to perinatal stress offer a valuable model for the study of the epigenetic mechanisms that drive a combined phenotype reminiscent of the comorbility among depression, schizophrenia, and drug addiction. Studies with rats or mice subjected to perinatal stress highlight the importance of a



particular metabotropic glutamate receptor subtype, the mGlu2 receptor, as a major target for epigenetic modifications occurring in response to early life stress. Drugs targeting mGlu2 receptors are currently under clinical development for the treatment of all major psychiatric disorders. It will be interesting to investigate whether "epigenetic" drugs, such as DNA demethylating agents, histone deacetylase inhibitors, or acetylating agents, correct the pathological programming induced by early life stress. At least one of these drugs, i.e., L-acetylcarnitine, has shown robust antidepressant activity in animal models and has proven efficacy in reversing the down-regulation of mGlu2 receptors associated with a depressive-like phenotype. Results of a project aimed at dissecting the molecular determinants of the epigenetic programming induced by early life stress may, lay the groundwork for new treatments directed at the core of the comorbility among depression, schizophrenia, and drug addiction.

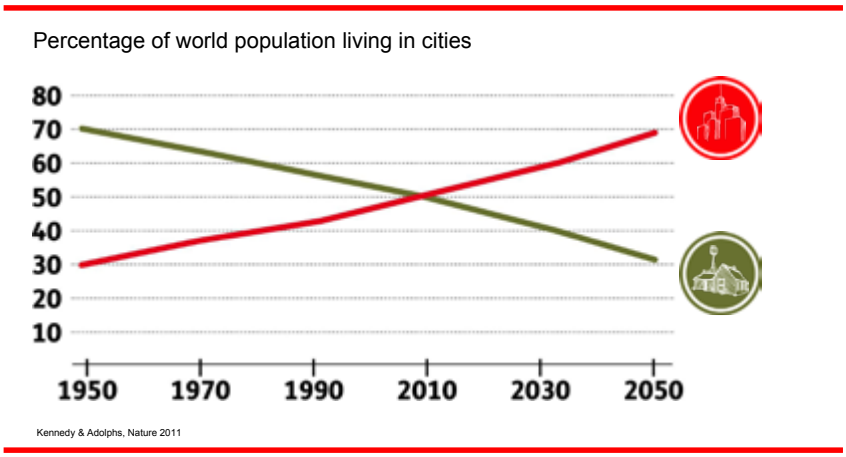
This Abstract reflects the collaborative research together with Prof. Stefania Maccari (LIA).I.

Mazda Adli

Urban Environment and the Brain: Stress and the City

Mazda Adli, Mood Disorders Research Group, Charité – Universitätsmedizin Berlin; Department of Psychiatry and Psychotherapy, Campus Charité Mitte; Fliedner Klinik Berlin, Center for Psychiatry, Psychotherapy and Psychosomatic medicine, Berlin, Germany

Urbanisation and its health impacts will be a major global challenge within the next decades and beyond. More than 50% of the world's population currently lives in cities. In 2050 about 2/3 of the global population will live in urban environments. Living urban is known to be a risk factor for (some but not all) psychiatric diseases such as major depression and schizophrenia. This is true even though infrastructure, socioeconomic conditions, education and health care services are better in cities. Available data indicate that it is urban living and upbringing per se, rather than other epidemiological variables that increase the risk



for mental disorders, point towards a causal relationship between urbanisation and mental illness. Social stress resulting from the combination of social density and social isolation seems to be the most important factor for the increased risk of mental disorders in urban areas. Recent studies have revealed that urban living and urban upbringing modify stress-dependent processing of emotions in healthy individuals as well as the grey material volume in defined cortical areas linked with stress vulnerability. Therefore, characterizing urban stress and investigating possible patho-mechanisms that translate into mental disorders, as well as developing preventative measures to protect mental health of people in urban environment is crucial. This can only be accomplished in a multidisciplinary approach between neuroscientific and urban research. We have proposed a "neurourbanism" to describe the joint methodological process in three different clusters:

- To explore the bi-directional relationship between built/social environments and behavior/emotion processing
- To explore the modulators of social stress in urban environments and to identify populations at risk for urban stress, e.g. through social isolation.
- To develop means in urban planning and architecture for the prevention of stress-associated mental-ill health in city dwellers and assess the health impact, stress impact and quality of life of housing and urban planning

Anna-Leena Sirén

Traumatic Brain Injury and Spinal Cord Injury

Anna-Leena Sirén, Experimental Neurosurgery, University of Würzburg, Würzburg, Germany

Traumatic insults to the brain and spinal cord due to falls or traffic and sport accidents are the leading cause of death and disability in Europe. Furthermore, such traumatic injuries due to falls have become an increasing health problem among the elderly. While mortality resulting from such injuries has been decreased in recent years due to improved emergency and hospital care, surviving patients often suffer from severe disabilities and may develop progressive brain damage and dementia of unknown origin. Animal and human studies suggest that diffuse axonal injury, excitotoxicity, mitochondrial and synaptic dysfunction, damage to the blood brain barrier and sustained neuroinflammation, all resulted by traumatic brain and spinal injuries, are of the major contributing factors to chronic neurodegeneration, demyelination, functional deficits and prevention of regeneration. Despite the intense research efforts in this area, effective therapies for brain and spinal injuries are still lacking. Further studies are needed to improve resolution of imaging of

cellular and functional events, taking into account differences in brain and spinal cord elastic properties and heterogeneity of the injury mechanisms. Repeated, long-term follow-up, in particular of mild repeated head injuries, while considering heterogeneity of injury, risk-factors, age and comorbidity, are necessary to improve validity of the studies and the rehabilitation strategies as well as the support of the development of effective treatments to confine injury progression and promote repair.

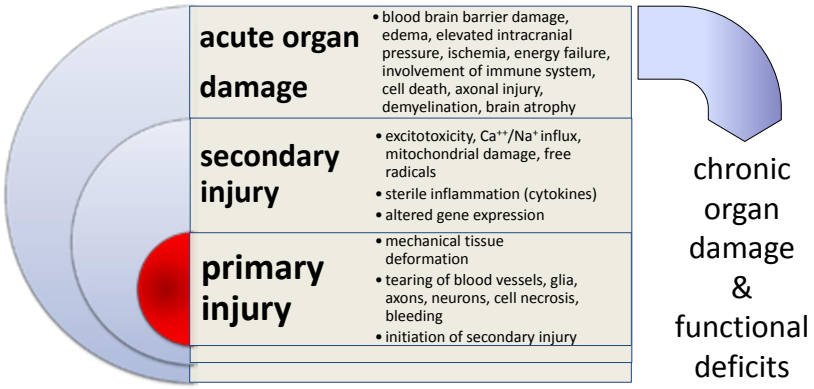


Figure 1. Pathophysiology of traumatic brain injury

François Berger

Rehabilitation, exoskeleton and brain-computer-interfaces

François Berger, Clinatec, Commissariat à l'énergie atomique, INSERM, Université Joseph Fourier, CHU Grenoble, France

A strong medical need propels the development of innovative technologies for neurological handicap resulting from traumatic injuries and neurodegenerative diseases. The newly available micro-nano-technologies "tool box" provides a unique opportunity for the first validations of the "brain-computer-interface" (BCI) concept. The first devices were developed for paraplegic patients where electrical activity of the motor cortex was recorded and motor action was obtained by specific algorithm driving a motor effector. Various strategies were developed all over the world, leading to devices, some less, some more invasive, such as EEG Helmet, ECoG arrays, or multielectrode intracortical arrays.

Although the clinical validation of the BCI concept had already attained in human subjects, clinical relevance and efficacy of BCI need to be improved. Sensorial feed-back, more integrated and wireless devices as well as exoskeleton effector should be developed. The Grenoble clinatec project developed for the first time a fully integrated

and wireless ECoG device as well as a four-arms exoskeleton, to maximize the clinical impact. The clinical trial using these devices is planned for 2015.

The approaching challenge will be the enduring biocompatibility issue, to be solved using innovative nanomaterials such as graphene or bioresorbable monofilaments.

In addition, ethical issues such as privacy of the electrophysiological data, legal responsibility, equal access to the technology and societal acceptance, need to be addressed promptly.

In conclusion, brain-computer-interface technologies are a perfect example of the success of technology responding to major health bottlenecks. European effort will have to encounter the sustainable translational technology research responding to major patient needs and the major ethical questions raised by these technologies.