ERA-NET NEURON II

Symposium

External insults to the nervous system

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Bucharest, Romania

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This Symposium is part of Work Package 2
Development of a Strategic Research Agenda
Work Package Leaders: Inserm and CNRS

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Welcome

Marlies Dorlöchter (Coordinator of ERA-NET NEURON, DLR-PT, Bonn, Germany)

The scientific symposium on "External insults to the nervous system" was introduced with a few welcoming words from Marlies Dorlöchter (DLR-PT, Bonn, Germany) on behalf of ERA-NET NEURON.

Marlies Dorlöchter

The main objective of ERA-NET NEURON is to address nervous system disorders and facilitate multinational funding of research of disease-related neurosciences. Since 2003 there has been an increase in funding of ERA-NET NEURON projects in this area. During the years 2012–2015, 24 funding organizations from 18 countries participated in the ERA-NET NEURON II program. Within the frame of ERA-NET NEURON II activities, Inserm and CNRS organized annual scientific workshops aiming for a better understanding the research areas that are under consideration for the topics of the Joint Transnational Calls (JTC) for proposals. The Scientific Advisory Board of ERA-NET NEURON also participates at these meetings, providing scientific advice regarding the call topics. The goals of the symposium in Bucharest included brainstorming about "External insults to the nervous system" to define the scope and exclusion criteria for the JTC 2016 and to verify that the capacity of the research community in the field is optimal.

The preparation of the Strategic Research Agenda (SRA) was a part of work package 2 of ERA-NET NEURON II, led by the French National Institute for Health and Medical Research (Inserm) and the French National Centre for Scientific Research (CNRS). The SRA, developed by the Scientific Advisory Board with input from external experts, aims to identify general scientific priorities as well as to understand disease mechanisms, disease progression, and interventions. Moreover, different nervous system diseases, including neurological diseases, psychiatric disorders, sensory organ diseases, and peripheral nervous system disorders, impose specific challenges that need to be addressed with appropriate tailored measures.

Introduction

Etienne Hirsch (Inserm, Paris, France) and Bernard Poulain (CNRS, Paris, France)

Etienne Hirsch (left) and Bernard Poulain (right)

Etienne Hirsch and Bernard Poulain provided the background for the symposium by listing causes for external insults to the nervous system, including toxic compounds that are particularly dangerous during perinatal life: viruses, bacteria, drugs and addictive substances; traumatic brain and spinal cord injury; and environmental threats. They introduced the aims of the symposium:

- To review epidemiological studies on environmental factors causing traumatic brain injuries (TBI) and the mechanisms of brain/nervous system toxic insults and infections
- To discuss the role of drug abuse, stress, psychiatric disorders, and brain development, as well as the role of societal and behavioral factors in brain disorders
- To review the causes and mechanisms of TBI and strategies for treatment
- To discuss the launch of a call for proposals on traumatic brain and spinal cord injuries

Epidemiological studies on environmental brain insults

Christina Hultman, Stockholm, Sweden

Christina Hultman started her talk by discussing the developing brain and vulnerability factors during childhood involved in the development of psychiatric disorders during adulthood including perinatal insults, parental characteristics, diet, in-vitro fertilization, and smoking during pregnancy as well as traumatic stress (e.g. the tsunami of 2004). It has been shown that the risk of developing schizophrenia, infantile autism, anorexia nervosa, Attention deficit hyperactivity disorder (ADHD), postpartum psychoses, and bipolar disorder, are associated with fetal growth restriction but also with low birth weight, small for gestational age, preterm birth, small head circumference and low American Pediatric Gross Assessment Record (APGAR) score. For example, there is evidence for an increased risk for developing anorexia nervosa in children born before 32 weeks of gestation.

Christina Hultman

The talk continued with questions concerning the factors related to maternal life style, including nutrition and alcohol consumption. The relationship between parents and infants is very important during the perinatal period and during the first years of life which may affect increased vulnerability to mental diseases. Conversely, parents of children with mental disorders can develop pathologies induced by their children's disorder. For instance, parents of children with autism have a higher probability to be treated for autoimmune diseases (e.g., rheumatic fever). Interestingly, Christina Hultman showed for the first time that there is a correlation between paternal age and the risk for the children to suffer from bipolar disorder as adults. In line with this, she also found an association between paternal age and both autism and schizophrenia. Another important risk factor for neurodevelopmental diseases is maternal nutrition during perinatal life. Thus, the crucial question is: what is the impact of environmental factors on the developing brain? Concerning environmental risk factors in schizophrenia, there are controversies and questions such as: what is the contribution of genetics versus environment? Is there evidence of causal associations between genetic and environmental factors? Could variations in schizophrenia outcomes between countries be due to differences in the diet? Is prenatal vitamin D

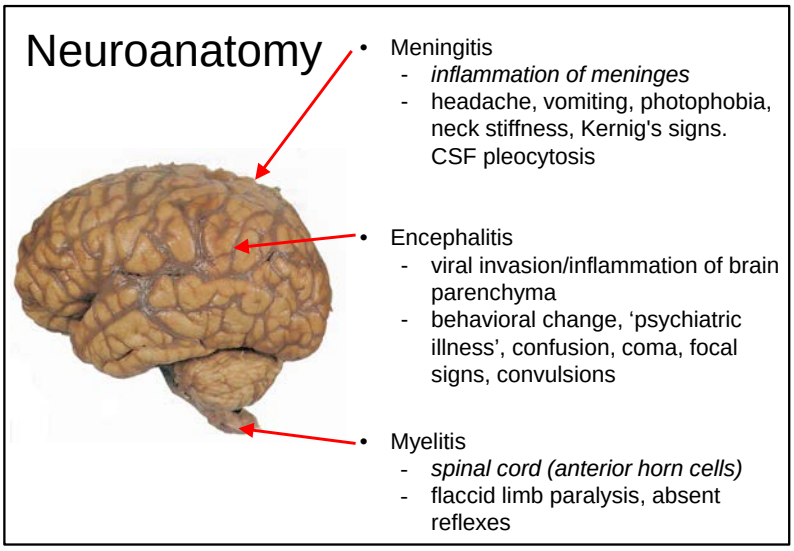
deficiency and its dietary supplementation during infancy related to the risk of schizophrenia? How can environmental pollution, such as dioxins and other factors impact brain development?
The discussion following the talk revolved around i) epigenetics, ii) the consequences of mother's smoking on the child , iii) the identification of biomarkers predicting the occurrence of psychiatric disorders in children depending on maternal characteristics and iv) how does the mother's mood influence the development of psychiatric disorders in the offspring?

Environmental brain/nervous system toxins and infections

Tom Solomon, Liverpool, United Kingdom

The talk began by asking the question what are the differences between CNS infections and toxin- induced damages. Viruses are the most common causes of meningitis which is an inflammation of the superficial layers of the brain tissue, the meninges. It is the mission of the Liverpool Brain Infection group, led by Tom Solomon, to tackle the issue of neurological diseases caused by infections and to reduce its global burden. The group aims to improve the understanding of the pathogenesis to enable innovation in diagnosis and therapy. Other goals are to develop a better patient management system, new treatment modalities and work with governments and the world health organization (WHO) to improve disease control.

Tom Solomon



The talk focused on examples of brain infections, a description of progress made in recent years and the possibility for future translational collaborative work through the ERA-NET NEURON. The herpes simplex virus (HSV) may cause cell damage by affecting mitochondrial transcripts. The genus Flavivirus, which belongs to the Flaviviridae family, contains some of the most important arboviral pathogens of man. The genus includes several aetiological agents of encephalitis, the most significant being Japanese encephalitis virus, West Nile virus and tick-borne encephalitis virus. Japanese encephalitis (JE) is one of the most studied arthropod zoonotic diseases, with 6-7 decades of human and animal research. JE research and public health policy in some Asian countries has exemplified the 'One Health' strategy aiming at optimal health for people, animals and the environment. However, despite significant mitigation of JE in Asian countries primarily due to vaccination programs and infrastructural development, JE continues to cause a major burden in the Asian region, as the vaccination program has not been developed in all countries. Arthropod-borne zoonotic infections such as JE represent one of the greatest challenges to animal and human health globally. The majority of exposed individuals will not develop disease, but a minority will develop a severe illness with a significant chance of permanent neurological damage or death. The factors that determine this selectivity for some individuals

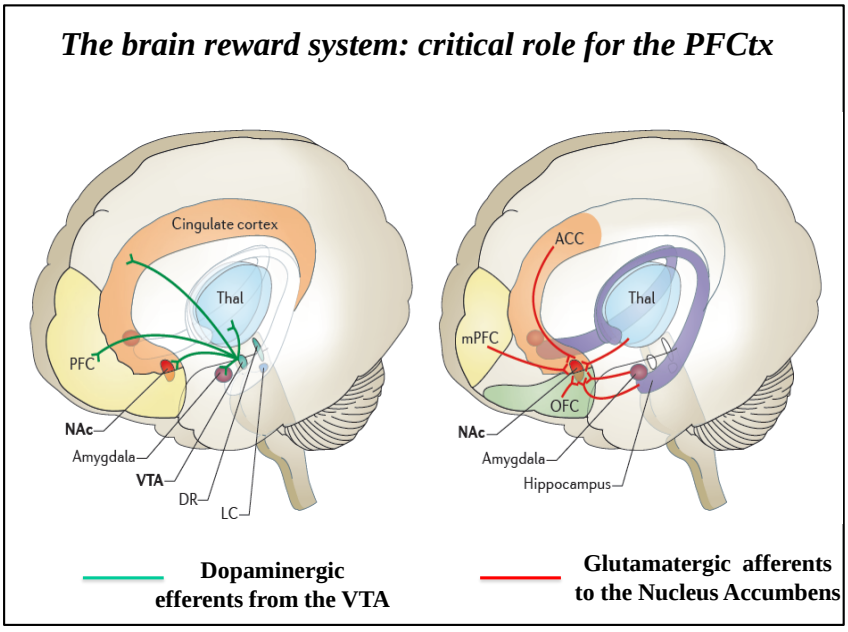
are numerous, involving complex interactions between virus and host and are still being actively studied. In many cases it appears that the host immune response, which is crucial to contain the virus and limit spreading to the brain, is also responsible for causing neurological damage. Innate immune responses can limit viral replication but may also be responsible for generating pathological levels of inflammation. Neutralizing antibody responses are protective but take time to develop. Vaccination in 11 new countries across Asia involving more than 200 million vaccinated persons reduced the number of cases by 854,000 and 214,000 deaths while saving 1.024 billion US$.

Drug abuse, stress, psychiatric disorders and brain development

Ferdinando Nicoletti, Rome, Italy

Early life events contribute to the pathophysiology of all major psychiatric disorders, including depression, schizophrenia, and drug addiction. The development of "pathological" epigenetic programming in response to early life stress may help to explain why these disorders are often associated and interdependent. Drugs that prevent or reverse the 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 comorbidity among depression-like behaviour, schizophrenia-like behaviour, and drug addiction. One established model of perinatal stress consists of the exposure of pregnant rats or mice to multiple episodes of restraint stress. This experimental paradigm is usually referred to as "prenatal stress" (PRS) but, at least in rats, it also causes early postnatal stress because it reduces maternal care in the first few days after birth, thus it becomes perinatal stress (PRS). It has been demonstrated that "PRS" rats consistently develop an anxious-depressive-like phenotype associated with abnormalities in glutamatergic transmission in the ventral hippocampus. These rats also exhibit abnormalities in the reward system and are prone to drug addiction. PRS mice have been proposed as a putative epigenetic model for schizophrenia. Indeed, in Chicago it has been shown that PRS mice develop epigenetic modifications of protein in the prefrontal cortex that are reminiscent of those observed in autopsy brain samples of schizophrenic patients. In addition, PRS mice display a psychotic-like behavioural phenotype characterized by abnormalities in sensory-motor gating, locomotor activity, and social interaction. Thus, PRS rats and mice represent a suitable model to study how

Ferdinando Nicoletti



early environmental stressors predispose individuals to psychiatric disorders and drug addiction. A common biochemical hallmark of PRS rats and mice is a reduced expression of type-2 metabotropic glutamate receptors (mGlu2 receptor), which are coupled to Gi proteins and are preferentially localized in presynaptic terminals where they decrease neurotransmitter release. At least in PRS mice, the reduced expression of mGlu2 receptors in the prefrontal cortex is already manifest during early postnatal development and is due to an increased promoter methylation of *Grm2,* the gene encoding the mGlu2 receptor. Drugs targeting mGlu2 receptors are currently under clinical development for the treatment of all major psychiatric disorders, including anxiety, depression and schizophrenia, and hold promise for the treatment of drug addiction. Interestingly, genetic variation of *Grm2* alters alcohol preference in animal models. Zhou et al. (Proc. Natl. Acad. Sci. USA, 2013) have found that selectively bred alcohol-preferring rats lack mGlu2 receptors because of a stop codon in the Grm2 gene (Grm2 *407). Taken collectively, these findings suggest that changes in the expression and/or function of mGlu2 receptors are common to depression/anxiety, schizophrenia and drug addiction, and that mGlu2 receptor agonists/enhancers or drugs that enhance the expression of mGlu2 receptors may correct the pathological phenotype caused by early life stress. Histone deacetylase inhibitors and the acetylating agent, L-acetylcarnitine, have been shown to enhance the expression of mGlu2 receptors in the CNS. In addition, L-acetylcarnitine displays rapid and sustained antidepressant-like activity in spontaneously depressed rats by up-regulating mGlu2 receptors in the frontal cortex and hippocampus.

Identifying 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 comorbidity among depression, schizophrenia, and drug addiction. In the discussion following Dr Nicoletti's presentation mechanisms of epigenetic drugs and microRNAs were addressed.

Urban environment and the brain: stress and the city

Mazda Adli, Berlin, Germany

There is a relative risk of schizophrenia related to urbanisation. Indeed, mental health problems are more frequent in urban than rural populations with a higher risk for urban versus rural populations of 39% for mood disorders and 21% for anxiety disorders. We have to consider that the percentage of the global population living in urban regions is growing dramatically and urbanization will be a major global change in the next 30 years. What is stress? Stress is an unspecific physical and psychological reaction of the organism to a challenge ahead. Stress was declared as one of the major health challenges of the 21st century. The response to stress consists in the activation of the neuroendocrine systems and it is modulated by different factors: genes and epigenetics, age, perinatal factors, personality traits, life events and urbanisation.

Mazda Adli

Urbanisation involves both social crowdedness and at the same time social isolation, and thus it is equivalent to a social stress. Social crowdedness leads to behavioural changes, irritability, mental disorders and higher mortality in many species not only in humans. Moreover, the quality of the social relationships can predict mortality. Among the neural substrates, amygdala activation correlates with city size. These are the premises to verify social stress as a hypothesis of urban stress: urbanisation is a source of stress inducing biological effects associated with mental diseases. Promising fields of future research are studies on inter-individual differences of stress vulnerability and identification potential high-risk populations (migrants, elderly, single). Also, it is important to identify different types and levels of urban stress and to understand the influence of the built environment on the emotional and mental wellbeing of the individual. To better understand the "interaction between mental wellbeing and urban environment", it is important to investigate the interaction between urban environments and social behaviour of inhabitants, including the effects of (child) adoption in urban settings, social participation as well as social fragmentation and segregation processes. However, despite the negative effects induced by stress in the city, "urban advantages" do exist as well. In this context, stress even acts as a protective factor in the cities! This concept is in agreement with the earlier definition of stress: a response of an individual to positive or negative stimuli. If we are not able to respond to stress in an appropriate way, we cannot survive.

How can we prevent negative urban stress? In order to respond to this last question it is important to investigate the effect of urban stressors on the developing brain and to develop measures for children and adolescents in order to increase access to the urban advantage. Thus, research on NEURO-URBANISM is of high relevance for our society. Promoting exchanges between urban planning as architecture and neurosciences is a very useful multidisciplinary approach to investigate the neurobiological impact of different modes of today's city life and to develop means in urban planning and architecture for the prevention of a stress-associated, negative impact on the health of urban populations.

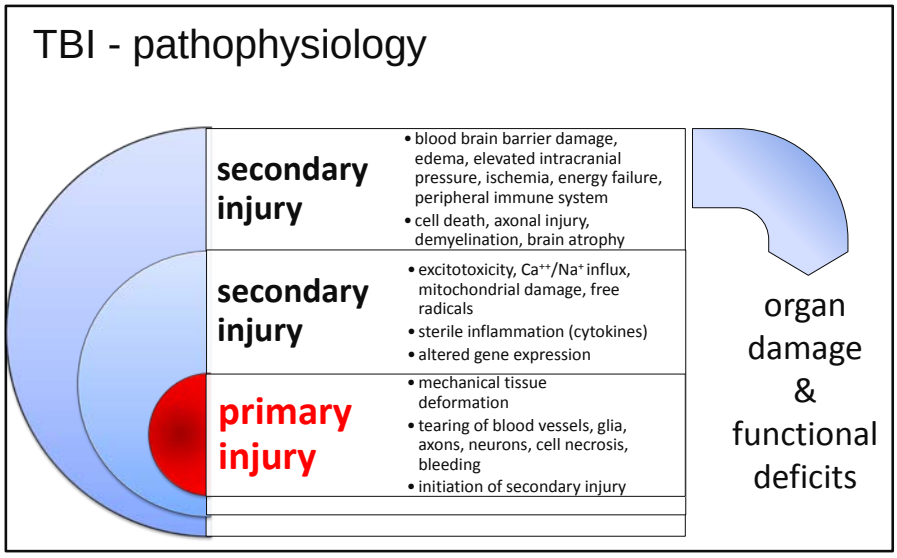
Questions from the audience were related to the impact of city pollution on the developing brain; how or what is the basis of social interaction; - the colour of the city and the importance of the green areas. And again, how can we correct negative urban stress? And how can we measure this stress response?

Traumatic brain injury and spinal cord injury

Anna-Leena Sirén, Würzburg, Germany


Anna-Leena Sirén

Traumatic brain injury (TBI) is defined as injury of brain tissue caused by an impact, penetration, or rapid movement of the brain within the skull. Each year, approximately 2.5 million people will experience some form of TBI in Europe; of these, 1 million will be admitted to the hospital and 75 000 will die." (Maas et al., Neurosurgery 2015, 76:67-80). The causes of this kind of trauma are often traffic accidents, falls and sport-related accidents with costs of about 50 billion Euros/year. Moreover, TBI is a risk factor for dementia and neuropsychiatric diseases.



The primary insult is usually a mixture of both focal and diffuse axonal injury. It has been possible to reproduce TBI in animal models for focal, diffuse + focal and diffuse injury. Concerning the pathophysiology of the primary injury, we can list mechanical tissue deformation, tearing of blood vessels, glia, axons, neurons, cell necrosis, bleeding and initiation of secondary injury. The secondary injury encompasses excitotoxicity and brain atrophy, resulting in organ damage and functional deficits. An important point in TBI is brain metabolism involving the energy-dependence of neuronal tissues (mitochondria, neuronal membrane potential, Sodium-Potassium ATP-ase, intracellular calcium). The concept of excitotoxicity involves a loss of ionic gradients in the presynaptic neuron, excessive glutamate release, glutamate transporter reversal, and release of magnesium block activation of extrasynaptic N-Methyl-D-Aspartate receptor (NMDAR) as well as calcium overload that will lead to cell death in the postsynaptic neuron. NMDAR have a neuroprotective function when located in the synapse but they mediate neurotoxic effects when they are located extrasynaptically. It is known that NMDAR play a role in the neurodegeneration in Alzheimer Disease (AD) and TBI with axonal damage including microtubule deficits inducing hyper-phosphorylation of tau and tau aggregation into neurofibrillary tangles. TBI also accelerates brain ageing. Indeed, it has been shown that the severity of neurodegeneration following TBI is influenced by age. In addition, TBI is influenced by regional differences in tissue elasticity, the functionality of blood brain barrier and by the severity of brain oedema. Recently, it has been demonstrated that Factor XII - an enzyme that plays an important role in blood coagulation - could be an interesting target for TBI recovery. In Factor XII-deficient mice a better rehabilitation has been observed, reduced neurodegeneration, and a reduction in cerebral microthrombi without increase in intracerebral bleeding. Finally, similar results have been observed with pharmacological inhibition of Factor XII. The clinical consequences of these molecular changes resulting from severe or mild TBI are variable chronic cognitive and/or neuropsychiatric impairments. Despite improvements in early acute care and intense research on patho-mechanisms there are no effective therapies to prevent neuronal degeneration associated to TBI. Thus, further studies are needed to take in account differences in tissue elastic properties, mild repeated head injury on synaptic function, improvements in resolution of imaging of cellular and functional events, heterogeneity of injury, risk-factors, age and comorbidity and repeated, long-term follow-up by analysing comorbidities. In parallel with TBI, Spinal Cord Injury (SCI) represents an important cause of neurodegeneration with primary, secondary and chronic injury phases. Recently, it has been shown that endogenous neural stem cells play a role in repair mechanisms after SCI. Strategies to stop injury progression and to promote repair consist of surgical stabilization and decompression, neuroprotection and neural regeneration (drugs, hypothermia, and diet), cell therapies and electrical stimulation. In this particular injury, further studies may consider rehabilitation parameters (electrical stimulation, timing, early mobilization), stem cells for therapeutic efficacy, safety issues, combination of

nanomaterials with cells/therapeutic agents, dietary interventions, and age and comorbidity. In summary, traumatic injuries are common, there is no specific therapy and the heterogeneity of injury is very important, since there are a lot of risk factors and comorbidity. A repeated and long-term follow-up of rehabilitation is necessary.

The following discussion focused on comorbidity between Parkinson and stroke as well as between epilepsy and TBI, the relationship between chronic TBI and tau pathology, and rehabilitation or compensation.

Rehabilitation, exoskeleton and brain-machine interface

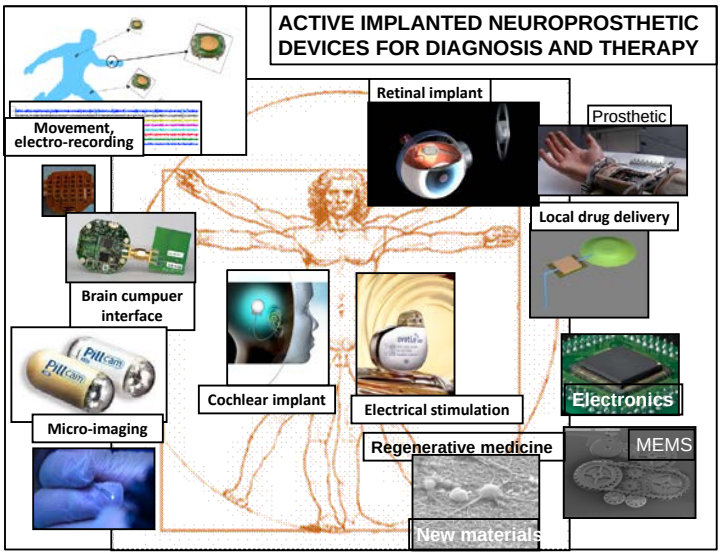
François Berger, Grenoble, France

In the context of traumatic spinal cord injury (TSCI) there is a strong need for biomedical research. TSCI is a catastrophic event. Usually sudden and unexpected, it is devastating and costly in human and social terms, with high medico-economic impact. Regenerative medicine is an important challenge for research on brain recovery of neural function. The new electronic technologies provide an important opportunity to study the possible interfaces between brain and computer (Brain-Computer-Interface, BCI).

François Berger

Today, it is possible to implant neuroprosthetic devices for both diagnosis and therapy. This concept was developed in the early 70's and the first neuroprosthetic device was implanted in humans in the mid-90's.

Since then, it has been possible to develop a new area of research on brain-computer interface strategies. One of the current BCI approaches is the measurement of brain electrical activity with an EEG helmet, electrocorticogram and a microelectrode array. It is possible to state that the concept is working and it is validated in human subjects. However, the technology still needs to be optimized. What are the future challenges in this particular area? Cortical implants are not compatible with long-term functionality and it is important to develop an integrated and wireless devices. In particular, a complete exoskeleton device, relevant in the clinical reality, is needed. This requires a translational biology approach. Biocompatibility research is under development coming from the clean rooms to the patients with a multidisciplinary team of technologists, biologists and physicians. One of the goals is to enable tetraplegic persons to perform movements like standing up, walking and opening a door through the use of an exoskeleton that is controlled by cortical activity: the patient imagines a movement, and a brain implant records and processes the electrical activity in the motor cortex in order to control the exoskeleton. Such approaches could solve the problem of long-term stability, advance the micro-nano-interface strategy, and develop new generation electronics. However, with these rapidly evolving technological innovations, it is also important to tackle the ethical aspects of human enhancement. In conclusion, biomedical engineering is a major opportunity for patient with handicap, but there are a number of problems that need to be solved, including the high costs for this kind of technology.



Annex

List of Participants

Speakers at the scientific workshop 'External insults to the nervous system'

1. **Prof. Christina Hultman,** Karolinska Institutet, Stockholm, Sweden
2. **Prof. Tom Solomon**, University of Liverpool, UK
3. **Prof. Ferdinando Nicoletti,** University of Rome, Italy
4. **Dr. Mazda Adli,** Fliedner Klinik Berlin, Germany
5. **Prof. Anna-Leena Sirén,** University hospital Würzburg, Germany
6. **Prof. François Berger**, Inserm, Grenoble, France

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2. **Prof. Francois Berger** (University of Grenoble, France)
3. **Prof. Christophe Mulle** (CNRS, Institut Francois Magendie, France)
4. **Prof. Fabrizio Tagliavini** (Istituto Nazionale Neurologico Carlo Besta, Milan, Italy)
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