neuron
Network of European Funding for Neuroscience Research

Scientific Workshop: "Frontiers in Neuroscience and prospects for their funding in Europe"

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ERA-NET NEURON

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SIXTH FRAMEWORK PROGRAMME

Contents:

The Workshop was introduced by a welcome word from the NEURON Coordinator: Dr. Marlies Dorlöchter, and followed by a round table in order to address several key points concerning the prospects for Neuroscience funding.

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Foreword

The neurosciences have a very large scope aimed at understanding how the nervous systems develops, functions and ages under normal and pathological conditions. The health challenges of neurosciences are well known given that disorders and deficits affecting the nervous system are common, often severe and, generally lack effective preventive or curative treatments. The scientific challenges are also huge due to the complexity that characterizes all levels of nervous system organization and which has to be analysed and integrated. However, breakthroughs are expected from major technological advances as well as multi-scale and multidisciplinary approaches. The first part of this workshop illustrated how technological and methodological advances can help answer several fundamental questions related to the normal and pathological function of the nervous system. The second part contributed to the understanding of how neuroscience funding is organized in Europe and in the US.

P Bovolenta illustrated the complexity of the organization of the nervous system and asked how such a system is accurately built during development. She illustrated how appropriate animal models can help understand the spatiotemporal regulation of gene networks, particularly the identification of cis-regulatory elements of transcription factors. Another important area is the repair of the nervous system and how one could take advantage of the potential of neurogenesis with stem cells.

D Choquet showed several spectacular applications of nanotechnologies combined with optics to trace single molecules in physiological (NGF, AMPA receptors) and pathological conditions (Alzheimer's disease). These techniques revealed an unsuspected complexity of the dynamic localisation of large molecules. New areas of optic research for improving spatial and temporal resolution were also discussed.

W Denk explained the potential of combining high resolution electron microscopy and image analysis for three-dimensional reconstruction of brain regions, visualizing the great complexity of its connectivity.

M Saarma addressed the question of the potential of neurotrophic factors for preventing degeneration or restoring the function of particular neuronal systems. This was nicely illustrated with the recently identified glial cell line-derived neurotrophic factor (GDNF) which is effective in animal models for Parkinson's disease.

L Cohen demonstrated that combining functional neuroimaging and neuropsychological paradigms in patients with specific lesions allows understanding the process of word reading which developed only very recently in humans. The adaptation for word recognition of brain areas, initially devoted to the visual recognition of objects, results in constrain due to their previous function.

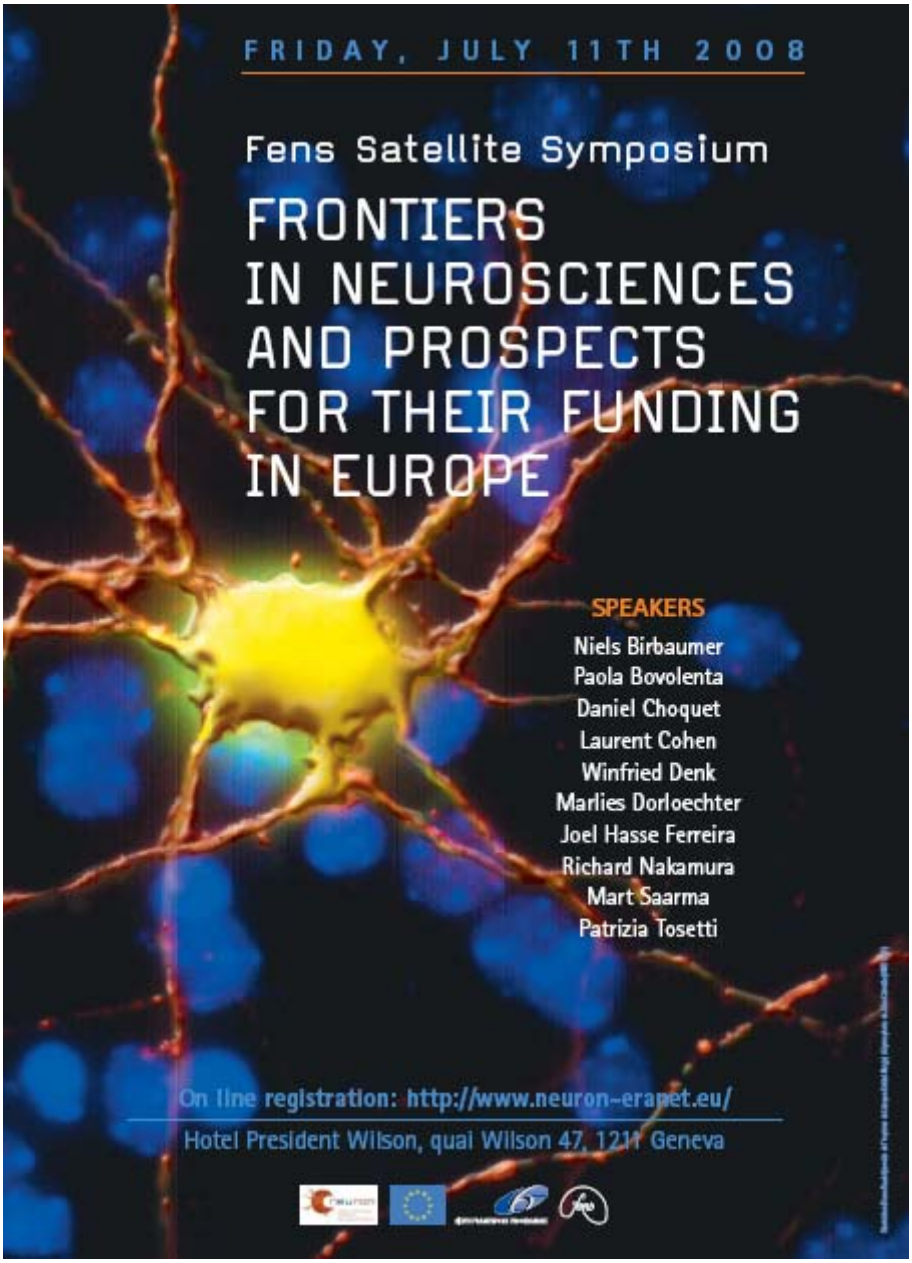
N Birbaumer gave an overview of the potential of brain computer interfaces to restore function or communication in brain-lesioned patients (patients with amyotrophic lateral sclerosis, locked-in syndrome or tetraplegia). Moreover, these interfaces may also be helpful for improving psychological and psychiatric disorders such as child Attention-Deficit Hyperactivity Disorder (ADHD).

In the second part of the workshop M Dorlöchter, P Tosetti and R Nakamura illustrated the major differences in funding strategies (top-down versus bottom-up), funding instruments and evaluation procedures among European countries and allowed comparing the organization and perspectives of neuroscience funding in the EU and in the USA (NIH). J Hasse Ferreira provided a testimony of his role at the Scientific and Technological Options Assessment panel of the EC parliament where Neuroscience research is highly considered.

This venue with excellent speakers has stimulated a lot of fruitful discussions with the scientists attending the workshop. It will also certainly contribute identifying new frontiers and challenges in neurosciences to support, with high priority and coordination, funding in these areas at both national and European levels.

Alexis BRICE
Inserm

Summaries of the conference



Prof. Paola Bovolenta

Spain.

TITLE: *"Advances and Challenges in Neuroscience"*

The brain is a complex system composed of about 10^{11} neurons for which individual connectivity can reach more than 10^{4} other neurons through chemical or electrical synapses. Such a network overcomes conventional description means and is difficult to describe even if innovative staining tools now allow for a better description of its three-dimensional structure as well as for a classification of its building blocks at the cellular and sub-cellular level. In this framework, the main goals of neurosciences are to understand how central nervous system is designed, how it works and finally, what are the exact origins of the numerous diseases that can impair it?

The latest advances in the field of neuroscience are strictly related to recent technological progress in imaging, genomics, proteomics, bioinformatics and bioengineering. For consistence and practical reasons, advances and concepts presented here will mainly rely on development associated with imaging as well as genomics. As an example, the mechanisms underlying the morphogenesis of optic vesicles in the medaka fish (*Oryzias latipes*) have been recently revealed, using a combination of cell-scale resolution imaging technique and transgenic procedures. Rx3 is a retina specific transcription factor. It has been associated with green-fluorescent protein (GFP) in a transgenic animal model and to a global red staining of all the cells nuclei. It has thus been shown that convergence and migration behaviour of retinal progenitor cells was controlled by Rx3. These results constitute a major breakthrough in the comprehension of organ formation cellular mechanisms (Rembold, 2006).

The knowledge of the central nervous system development is essential to understand how it is built, how it functions and how it can be restored. If important embryological data are by now available to describe this development, signalling factors effects and mechanisms as well as their sources and destination interactions remain largely unknown. The growth of numerous regions of the brain is controlled by a few signalling molecules. This has been shown in the differentiation process of dorsal interneurons and ventral neurons of the roof plate and the floor plate of the developing spinal cord in vertebrates. Similarly, the combination of fibroblast growth factor (FGF) delivery by a specific organizing centre with sonic hedgehog (SHH) can explain the differentiation of the retinal ganglion cell (RGC) and thus the retina neurogenesis in birds and fish. Its action on RGC consists in a negative regulation of growth cone movement in a specific way. It does not interfere with RGC proliferation rate or differentiation. SHH thus guides RGC axons growth along ventral midline. The SHH is more generally required for a large number of developmental processes like, bilateral eye field formation (Chiang, 1996; Varga, 1999), proximo-distal axis and dorso-ventral patterning of eye (Huh, 1999), retinal proliferation and differentiation (Wallace and Raff, 1999; Zhang and Yang, 2001), normal laminar organization in the retina (Wang, 2002), optic disc and stalk development (Dakubo, 2003; Morcillo, 2006), astrocytes proliferation in the optic nerve (Wallace and Raff, 1999), lens regeneration (Tsonis, 2004), proliferation and migration of optic nerve oligodendrocyte precursors (Merchán, 2007) and control of the movement of RGC axons in the chick (Trousse., 2001).

Among the fundamental remaining questions, one has to know how cells interpret the same signal in a different manner and also how a given cell integrates different and in many cases, opposite information. A simple way to address this question is to admit that cells can sense signaling molecules concentration differences as well as their combination. If the answer seems undemanding, proving it is not an easy task at all.

At a more general level, one can think that phenotypic variability underlies the combination of similar building blocks across species but following different genetic pathways. That has been shown in the homologues eyeless/Pax6 genes. Indeed, in mice and humans the single Pax6 gene appears to encode both specification and growth controlling proteins (Rodrigues, 2004) but it also plays a major role in drosophila eye development. The genes expressed in these pathways are under the control of cis-regulatory elements or modules which constitutes a higher level of genetic information. As written by Davidson and Erwin: "*The genetic program directing the development of a single cell fertilized egg into an sea urchin embryo is encoded in the organism's genomic DNA. The essence of this program is a network of genes encoding transcription factors and the cis-regulatory modules controlling the expression of those genes. Each module can receive multiple inputs at multiple sequence specific target sites for other transcription factors in the network, and these signals are integrated into a single output resulting in the gene being turned on or off in different areas of the developing organism at different points in time. Understanding the developmental process therefore requires finding the functional linkages of the network - connecting the output of regulatory genes to the genomic target sites to which those products bind to activate further rounds of specification. This task is made challenging by our incomplete understanding of how transcription factors discern functional target sites from the vast population of non-functional sites with the same sequence in the genome.*" (Davidson and

Erwin, 2006). These concepts are well illustrated by a recent work on the combination of seven different cis-regulatory modules in medaka. The Six3 is an important regulator of vertebrate forebrain development. Clusters of highly conserved noncoding regions surrounding this Six3 gene have been identified and thus, the transgenesis of these sequences in medaka have shown that these sets of cis-regulatory elements are collectively responsible for the precise spatio-temporal organization of regulatory gene networks. (Conte and Bovolenta, 2007).

The healing of brain or spinal injuries is a major application of neurogenesis investigations. Indeed, new neurons are constantly produced during adulthood in several brain areas like olfactory bulb (OB), rostral migratory stream (RMS) and sub-ventricular zone (SVZ). Several questions arise then: Is neurogenesis restricted to these brain areas? Does a brain lesion activate neurogenesis? Do the new cells contribute to brain repair? Can the brain produce different cells types in response to different lesions? Can we activate and exploit neurogenesis for therapeutic purposes? Can we take advantage of embryonic neurogenesis to repair a damaged CNS? Several recent studies have proven that such regions like human cerebral neocortex was not able to generate new neurons during adulthood, at least at a detectable level (Bhardwaj, 2006) whereas other brain areas like SVZ were able to produce newly incorporated neurons in a damaged striatum after a stroke (Yamashita, T., 2006). Besides, in monkey and after a spinal cord injury, neural stem cells have given rise to astrocytes and oligodendrocytes that localize the lesion site (Yang, 2006). Taking all these information into account, it seems rational that a better understanding of embryonic neurogenesis mechanisms could help us to repair damaged central nervous system. For example, under certain conditions, transplanted cells of a retina donor can integrate and differentiate into rod photoreceptors in an adult patient affected by a photoreceptor degeneration disease (MacLaren, 2006).

All these findings show us that exploiting the potential of stem cells is a great challenge for future therapies, but beyond the scientific knowledge that is daily produced, we need to find ways to integrate and channel in an effective way the overwhelming amount of information which is generated by the increasing amount of neuroscientists in order to really exploit its full potential. In addition, we have to improve scientific communication and spreading and we need to convey information to the general public in a more effective and educated way, to give precise messages, without taking away hope for future cures nor to give false expectations or create false impressions.

Dr. Daniel Choquet

France.

TITLE: *"Nanoscience and optic to understand synaptic transmission"*

The synapse can be defined as a contact area between two neurons. In the pre-synaptic region, an electric current induces the release of neurotransmitters in the synaptic cleft. These neurotransmitters can bind to a post-synaptic receptor and thus produce a second electric current responsible for post-synaptic cell electrical activity. Synapses are very numerous structures. As shown with specific staining (HOMER for post-synaptic and synapsin for pre-synaptic region) they cover neuron bodies and neurites. Thousands of them can be present on one cell and since neurons are very abundant in the central nervous system as well, the resulting connectivity structure is highly complex. The synapse structure itself and its presynaptic and postsynaptic components are by now well described. Nanoscale views of the synapse exhibit a tight region with a dense protein distribution (Siksou, 2007; Kennedy, 2000) and synaptic protein structures are finely described as well as most of their interactions and functioning.

However, the description of these subcellular structures remains static. It has been known for a long time now that synapses allow special kinds of plasticity and are thus dynamic structures. The most prominent experiment of such dynamic properties underlines the long term potentiation (LTP) and long term depression (LTD) occurring in the glutamatergic synapses of the hippocampus. In this experiment, electrical stimulation of the neurons produces long lasting changes in synaptic transmission which are known to underlie learning and memory. The understanding of the synapse dynamics is consequently a key point since major diseases such as depression, addiction, dementia, anxiety disorders, schizophrenia, migraine, stroke, epilepsy or Parkinson are related to disorders of synaptic transmission. The question is then "How to reconcile the complex and precise structural organization of the synapse with its tremendous plasticity?"

In a recent past (until 1998), the synaptic receptors renewal timescale was of several hours. Between 1995 and 2000, new studies have shown that this timescale could be reduced to several minutes. Finally, at the turn of the century it has been shown that the time necessary to remove or deliver synaptic receptors was closer to several seconds. New techniques based on nanotechnology are necessary to investigate such mechanisms at the molecule level with a second timescale resolution. Markedly nano-optics brings main improvements to classical neuroscience tools like a single molecule detection approaches which demonstrates the ultra-dynamic nature of synaptic components. Since the only way to catch synapse dynamics is to have a closer view at the molecule trafficking in real-time, dedicated technologies have been developed from 1976 when the fluorescence recovery after photobleaching (FRAP) was the first method for the analysis of receptor movement. Immuno-based techniques have then allowed the tracking of single particles and more recently of single molecules and nano-particles like quantum dots or metallic particles. The quantum dot is a core nanocristal covered with both an anorganic shell and an organic shell and it has the capability to link to a single specific molecule through Fab anti-IgG and IgG anti-receptor. This technology has been successfully used to show or understand many cellular and sub-cellular mechanisms in neuroscience.

The retrograde axonal transport of nerve growth factor (NGF) signals is critical for the survival, differentiation and maintenance of several subpopulations of neurons but the mechanisms underlying this transport are poorly understood. The use of dot-labelled NGF has allowed to track the movement of NGF in real-time in rat cultures of dorsal root ganglion. Surprising results have been obtained at this occasion and markedly that a large majority of NGF vesicles only contains 1 dimer. Such findings point to the possibility that a single NGF dimer is sufficient to sustain signalling during retrograde axonal transport to the cell body (Cui, 2007).

In a healthy neuron, the tau protein can be distributed in a proximal-distal (from cell body to synapse) gradient that allows kinesin-driven anterograde transport from the cell body whereas in Alzheimer's disease, it accumulates at the soma and consequently inhibits it, leading to synapse degeneration. Kinesin and dynein are motor proteins in charge with transport of cellular cargoes toward opposite ends of the microtubule tracks. Single molecule studies of these motor proteins moving along tau-decorated microtubules have shown their action were inhibited at different concentration of tau protein suggesting that microtubule associated proteins (MAP) like tau could regulate microtubule dependant axonal transport (Ram Dixit, 2008). The understanding and treatment of Alzheimer's disease are major challenges for neurosciences in the next decade and in this context, the use and development of nanotechnologies will surely have a large impact on it.

Glutamate is the major fast excitatory neurotransmitter in the central nervous system and the understanding of its functioning thus requires a fine knowledge of its properties and of its receptors like AMPARs (AMPA receptors) as well. Real-time imaging studies of quantum dot stained AMPARs show that part of them is immobile whereas the other part is spontaneously mobile laterally in the membrane. Additional electrophysiological studies based on high frequency stimulation demonstrate that this mobility plays a crucial role in post-synaptic depression occurring after high-frequency stimulation and as a consequence, the

regulation of postsynaptic receptor mobility affects the fidelity of synaptic transmission by shaping the frequency dependence of synaptic responses. This phenomenon is tightly linked to memory and learning mechanisms is therefore of major importance from both a fundamental and a clinical point of view.

The future of nano-optic technology is promising since this is the first tool ever than allows real-time *in vivo* visualisation of molecular dynamics in a specific way. A large number of questions can be then addressed with this method like the localization of individual synaptic components at nanometre resolution in living neurons (e.g. PALM for Photo-Activated Localization Microscopy or STORM for STochastic Optical Reconstruction Microscopy), the development of nanoscopy to perform bulk measurements at nanometre resolution (e.g. STED for Stimulated Emission Depletion) or the manufacturing of new neuron activity reporter probes. Besides, these tools can be used to determine the molecular basis of synaptopathies.

The PALM and STORM technologies make use of dark fluorophores than can be turned into a fluorescing state using a flash of light. The molecules are thus turned on at a times to break the diffraction barrier. Once this has been done for every molecule, the precise localisation of the light source is localized by fitting its point spread function (PSF) and thus computing its exact centre which allows a 20 nm resolution.

The STED method uses two laser sources and a confocal laser scanning microscope. The first source (excitation pulse) is immediately followed by the depletion pulse of the second source. The second pulse is spatially arranged into a "doughnut" mode and thus selectively inhibits the fluorescence at the outer parts of the initial pulse image since its lower energy photons quench the molecules of this area to the ground state by stimulated emission. The fluorescence of the doughnut centre remains of course unaffected and spatial resolution can reach 10 nm.

Prof. Mart Saarma
Finland.

TITLE: *"Biology and Therapeutic Potential of Neurotrophic Factors"*

During development, neurons are overproduced and their excess is removed by programmed cell death (PCD) during target innervation. In the peripheral nervous system (PNS) this process is controlled by growth factors (GF) called neurotrophic factors (NTF). This phenomenon is, however, poorly understood in the central nervous system (CNS) and this is a challenge since neuron death and its related mechanisms are important issues in neurodegenerative diseases. There is emerging experimental evidence that also in the CNS NTFs may control the number of neurons and play a role in maintaining neuronal networks.

The glial cell line-derived neurotrophic factor (GDNF) family is one of the three main NTF families (Bespalov & Saarma, 2007, Airaksinen & Saarma 2002, Andressoo & Saarma, 2008). GDNF promotes the survival of motoneurons and can protect and regenerate dopamine neurons (DA) in animal models of Parkinson's disease (PD). The loss of dopaminergic (DA) neurons in the nigrostriatal pathway induces slowness of movement, resting tremor, rigidity and postural instability in PD patients. At the initial stage of the disease already more than 60% of the DA neurons are lost (Dauer & Przedborski, 2003). The current therapies of PD are alleviating symptoms and do not slow down the degeneration of DA neurons. Therefore, future therapies should include (i) prevention of the DA neurons degeneration as well as (ii) increase of the functional activity of the remaining DA neurons.

Neurotrophic factors or small molecules mimicking the action of NTFs are candidate drugs that can be potentially efficient against PD but one of the first problems to address is the drug delivery. The systemic delivery of drugs has two major problems: (i) the side effects and (ii) the blood-brain barrier. There are several techniques that can be used to circumvent these problems. Concerning the delivery of biological factors behind the blood-brain barrier, there are two possibilities: (i) the use of mechanical pumps and (ii) the gene therapy (use of viral vectors for example). Both techniques have pros and cons and an innovative compromise could be the encapsulated biodelivery system. It consists in a thin (1mm) implantable device containing a cell matrix enclosing living cells of stable genetic expression and producing continuously the required drug for example a NTF. The membrane that separates both compartments are semipermeable and immunoisolatory. This system is removable if necessary.
In the first clinical trials on PD patients GDNF was infused intraventricularly. This caused adverse effects and besides the motor score was not improved since GDNF reached neither the caudate putamen nor substantia nigra (SN). In two independent phase 1 studies GDNF was infused with the pump into the patient's caudate putamen. These studies demonstrated that GDNF has therapeutic potential (Gill et al., 2003; Slevin et al., 2005)). However, as in the following phase 2 study GDNF had no clinical benefit, and neutralizing GDNF antibodies were detected in patients (Lang et al., 2006) GDNF clinical trials were terminated.

Our current approaches follow two directions: (i) search for new NTFs and (ii) development of small molecules which mimic the activity of NTFs. We first asked the question: are there still new uncharacterized NTFs? We have recently discovered a new neurotrophic factor called conserved dopamine neurotrophic factor (CDNF) (Lindholm et al., 2007) which together with mammalian mesencephalic astrocyte-derived neurotrophic factor (MANF) and invertebrate MANF/CDNF homologous protein form a new family of NTFs. Human CDNF and MANF have recently been produced using either bacterial expression systems or baculoviral infection in Sf9 insect cells. CDNF immunohistochemistry has revealed its presence in numerous brain areas including cortex, hippocampus, substantia nigra, Purkinje cells, cerebellum and locus coeruleus. CNDF has then been tested *in vitro* where it does not promote the survival sympathetic and sensory neurons. Rather, it is the most CNS-specific neurotrophic factors known, virtually with no *in vitro* effects on the PNS neurons. However, CDNF has both neuroprotective, as well as neurorestorative effects in *vivo* on DA neurons in the rat 6-OHDA model of Parkinson's disease. Importantly, CDNF not only protects dopamine neurons, but also protects and repairs degenerating TH-positive striatal fibres in substantia nigra. CDNF also restores motor function in 6-OHDA lesioned rats. The results suggest that CDNF is a novel evolutionarily conserved protein that together with MANF forms a novel family of neurotrophic factors. It is the most CNS-specific neurotrophic factor known, virtually without *in vitro* effects on the PNS neurons. It protects dopaminergic neurons against 6-OHDA lesion *in vivo* probably better than any other known protein. Most importantly, CDNF repairs the nigrostriatal dopaminergic system and therefore, it has a good potential as a therapeutic protein for the treatment of Parkinson's disease. Future work on this topic will include the study of knockouts (KO) and conditional knockouts of CDNF and MANF, the search for the CDNF and MANF receptors, and analysis of their signalling pathways. Future studies on the elucidation of CDNF and MANF therapeutic potential will include experiments with the mouse MPTP model, experiments with the genetic PD models, experiments with different methods of delivery like adeno-associated virus (AAV) or minipumps and GMP production of CDNF-AAV and CDNF protein.

Prof. Laurent Cohen

France.

TITLE: *"Neuropsychology and imagery of word reading: footprints of culture in the brain"*

Described by Dejerine in 1892, the pure alexia is a neuropsychological syndrome, typically following brain injury and consisting in an inability to read: "*The patient suddenly observed that he could not read a single word, while he could write and speak quite well, and could distinguish as clearly as before all the objects and persons which surrounded him*". The fact that there exist selective reading deficits following localized brain damages is evidence for the existence of a paradoxical "*cerebral organ*" devoted to reading. Paradoxical since reading is a very recent cultural invention (at most 5400 years) and there hasn't been enough time or pressure for biological evolution to design a so-called "*reading area*" in the brain. Yet pure alexia is evidence that in literate adults there is a cerebral specialization: a system necessary only for reading and the question is: where does this system come from?

It is commonly accepted that the human brain possesses, by virtue of its innate organization, a visual system, a language system and a number of other devoted systems. But reading is a recent cultural invention, with no specific innately defined cerebral basis. So what do we learn when we learn how to read? On the one hand we take advantage of the property of the language system to represent speech as a string of discrete successive units such as phonemes, syllables and words, and on the other hand we take advantage of the property of the visual system to group and identify objects and to the invariant recognition of letter strings. We essentially learn how to articulate these two systems, by creating associations between pieces of speech (phonemes, syllables, etc) and small visual objects (letters, words, etc). This presentation is a brief overview of some of the things we know about the point of contact of the visual and the verbal system in reading.

The first stage of word reading is the computation by the visual system of a representation of letter strings invariant, regardless their colours, font, case position features ... This results in the construction of a visual word form (VWF) which is the main input to the language system and accesses the meaning, computes an articulation program, etc... Models of the "*visual word form system*" postulate that a left occipitotemporal region implements the automatic visual word recognition required for efficient reading.

This theory was assessed in a patient in whom reading was explored with behavioural measures, fMRI, and intracranial local field potentials (from Gaillard, 2006). Prior to surgery, when reading was normal, fMRI revealed a normal mosaic of ventral visual selectivity for words, faces, houses, and tools. Intracranial recordings demonstrated that the left occipitotemporal cortex responded with a short latency to conscious but also to subliminal words. Surgery removed a small portion of word-responsive occipitotemporal cortex overlapping with the word-specific fMRI activation. Following surgery, the patient developed pure alexia with letter-by-letter reading, while he showed no impairment for other categories of visual objects. Left ventral activations induced by briefly presented words disappeared, while activations related to other categories of objects persisted. The conclusions of this study are (i) that the VWF area (VWFA) is necessary to expert reading and (ii) that it is necessary only to reading.

Several other fundamental results have to be taken into account regarding VFWA which improve our comprehension of the reading mechanisms. Written words can receive nonconscious semantic processing more easily for emotional words like "danger" than for neutral ones like "sonata" (Naccache, 2006). The letter strings are represented in the VWFA in an abstract visual format independent of case and font (Dehaene, 2001).The VWF system is invariant for large and arbitrary changes in the shape of letters (Qiao, in preparation). The VWF is invariant for script changes. This has been shown using Kanji and Kana words which are equivalent at the lexical level (Nakamura, 2005). All these recent studies highlight that the VWFA is attuned to specific features of the familiar script: (i) letters are represented in a format invariant for culture-dependent changes in shape and (ii) it is sensitive to language-specific orthographic regularities.

Strings of letters are complex objects which are usually coded in the ventral visual pathway through a hierarchy of converging detectors, increasing invariance, and tuned to more and more complex *stimuli*. The resulting computational system looks like an extension of the feed-forward architecture suggested by Hubel and Wiesel in 1968 (Serre, 2007). Besides, in the ventral visual stream, a posterior-to-anterior hierarchy of neural processors has been revealed (Dehaene, 2005), with increasingly larger receptor fields, tuned to increasingly more complex word fragments (from bars, letter fragments, letters, abstract letters, bigrams and finally to word fragments). Such a posterior-to-anterior gradient of detectors was observed through the entire span of the occipitotemporal cortex, with activation becoming more selective for higher-level *stimuli* toward the anterior fusiform region. A similar gradient was also seen in left inferior frontoinsular cortex. Those gradients were asymmetrical in favour of the left hemisphere. As a result, the left occipitotemporal VWFA should not be seen as a homogeneous arrangement but rather as a structure with a high degree of functional and spatial hierarchical organization which results from a tuning process during reading acquisition (from Vinckier, 2007).

Conclusion: human being adapts to word recognition brain areas which are initially devoted to the visual recognition of objects in general. The capacities and limits of those prior biological functions constrain the acquisition of this novel cultural competence. Ongoing progress in neuroimaging techniques gives us an increasingly precise understanding of the normal and impaired mechanisms of reading and other crucial culture-dependent abilities.

Prof. Niels Birbaumer

Germany.

TITLE: *"Brain Computer Interfaces: Applications in Paralysis and Emotional Disorders"*

A few years ago, new experimental tools have been created, aiming at tightly interfacing brain and machine in a closed-loop environment (Nicolelis, 2001). It usually consists in a multichannel acquisition system connected to selected areas of the brain, a real-time processing signal unit able to extract information of neuronal activity and finally a real-time interface able to communicate with external devices. The second part of the loop consists in a sensory-motor unit including an effector (i.e. a three-dimensional artificial limb) as well as proprioceptive and exteroceptive sensors which provide sensory feedback to the brain. This closed-loop conception is related to classical control theory and is the basis for most of the Brain-Machine-Interfaces (BMI) or brain computer interface (BCI) so far. For example a similar setup (brain signal acquisition, real-time signal processing and device command) allows paraplegic patient to directly control their wheelchair with their cerebral activity (Wolpaw, 2002). In this case, the patient has to learn how to control the device taking benefit of the closed-loop system. The learning appears in the long-term modification of the slow cortical potentials which are interpreted by the interface to move the wheelchair.

Based on the same principles, an innovative approach to cure child Attention-Deficit Hyperactivity Disorder (ADHD) has been developed using BMI. The patient has to train to control computer visual cursors (this indirectly means that he has to self-regulate his own slow cortical potentials). This behavioural therapy is an alternate to the use of drugs and already offers good results (Strehl, 2006). The use of electromyography (EMG) is also a good alternate when people can still have a muscular activity. It can even be applied to muscles like sphincters.

The detection of cognition can also be performed with similar systems. People with amyotrophic lateral sclerosis (ALS) or Guillain-Barré syndrome (Birbaumer, 2002) have shown the ability to perceive and process various aspects of their environment, including, in some cases, semantic elements of human speech. Besides, people with locked-in syndrome have also been able to communicate through a clever BCI (Birbaumer, 1999). Recent progress have also been made using BCI improving the spatial resolution and the access to communication in complete paralysis, locked-in syndrome, and motor restoration (Hinterberger, 2008). Additional studies have shown that such patients may be affected by depressive syndromes. However, it is also established that (i) those syndromes are often overestimated and that (ii) these patients frequently remain free of depression and maintain a good quality of life despite their disease. This is very encouraging in the quest for new communication methods between them and their environment (Kübler, 2005).

Imaging methods have shown the possibility to discriminate and to map in the brain, the effects of emotional *stimuli*. This efficient tool has provided crucial results to help paralysed people interacting with their environment: (i) the increased activity in localized motor networks might be used to control brain-computer interfaces to drive communication and limb prosthetic devices in patients with loss of motor control such as severely disabled amyotrophic lateral sclerosis patients in a locked-in-like state (from Lule, 2007) and (ii) fundamental information like hand movement direction can also be decoded from magnetoencephalography (MEG) and electroencephalography (EEG) (Waldert, 2008). More recently, a MEG based BCI has been developed (Buch, 2008) which has been applied to people suffering severe cases of motor impairments following strokes. After training, it has been shown that a volitional control of neuromagnetic activity could be used by the patient to perform very difficult tasks like the control of grasping through a mechanical hand orthosis.
Psychology and psychiatry can also be investigated using BCI. It has been shown for years now that psychopaths had specific physiological responses (EMG) to emotional *stimuli* (Patrick, 1993). More recently methods of brain activation based on functional magnetic resonance imaging, electrodermal responses, emotional valence, arousal, and contingency ratings have also established that dissociation of emotional and cognitive processing might be the neural basis of the lack of anticipation of aversive events in criminal psychopaths (from Birbaumer, 2005). To summarize, the feeling of fear or guilt is generally lower in psychopaths compared to other people. FMRI-BCI based systems including support vector machine (SVM) classifiers and visual feedback and reward computation are also successfully applied to the study of schizophrenia. They allow for operant conditioning in humans and the related training has shown that the functional connectivity could changes thanks to this BCI.

All these methods show that BCI makes possible (i) to have a deeper and dynamic understanding of the brain functions and of their mapping as well as (ii) to provide new issues to cure, help or restore brain damages or illnesses since these systems allow for long-lasting changes in central nervous system functional connectivity. The non invasive methods presented here make them incontrovertible in clinical applications for human patients. Indeed, invasive approaches present too many drawbacks incompatible with human health and long lasting application.

PD Dr. Marlies Dorlöchter

Germany.

TITLE: *"Funding of Neuroscience in Europe: the ERA-Net NEURON"*

A European Research Area (ERA)-Net is a new funding instrument of the European Community (EC) in Framework Programme 6 (FP6). It aims at cooperation and coordination of national or regional funding programmes and its main participants are Ministries and funding agencies. EC members present high discrepancies in their national public funding for research, which is widely fragmented and consequently needs restructuring in order to be more efficient and synergistic. NEURON is the acronym for Network of European funding for Neuroscience research in the area of disease related neurosciences. The ERA-Net aims at overcoming fragmentation of funding programmes.

The NEURON partners are:

- Austria, Austrian Science Fund (FWF)
- Finland, Academy of Finland (AKA)
- France, French National Centre for Scientific Research (CNRS)
- France, National Institute for Health and Medical Research (INSERM)
- France, Agence Nationale de la Recherche (ANR)
- Germany, Project Management Agency in the German Aerospace Centre and (PT-DLR) for the Federal Ministry of Education and Research (BMBF)
- Israel, Chief Scientist Office-Ministry of Health (CSO-MOH)
- Italy, Ministry of Health (MOH)
- Luxemburg, National Research Fund (FNR)
- Poland, National Centre of Research and Development (NCBiR)
- Romania, Ministry of Education and Research (MEdR)
- Romania, National Centre for Programmes Management (NCPM)
- Spain, Institute of Health Carlos III (ISCIII)
- Spain, Ministry of Science and Innovation (MICINN)
- Sweden, Swedish Research Council (SRC)
- United Kingdom, Medical Research Council (MRC)

Among the most important and difficult NEURON activities is combining national budgets and launching calls for proposals in order to jointly provide financial support for European transnational research consortia. The first NEURON joint call has been published in January 2008 on the topic of neurodegeneration. Twelve research consortia were selected in a peer-review process and will be funded as of the beginning of 2009.

NEURON activities also include (i) conducting foresight activities, (ii) building a link between neuroscience researchers and society (general public, policy makers), (iii) supporting young scientists, and (iv) benchmarking national procedures in research funding and measures to promote technology transfer or translational research.

Compiling knowledge about national programmes and funded projects is also part of the NEURON work. A recent survey on "European Funding Programmes for Neuroscience Research" has been conducted on questions like: (A) funding principles and strategies, (B) funding instruments, (C) evaluation process and (D) budget. 87 funding organizations have been contacted and asked to answer respective questions. More than 50% of them (45/87) have sent back the questionnaire and eventually, 33 funding organizations from 20 European countries and Israel could be analyzed:

(A) Important discrepancies exist between funding organisations concerning funding principles and strategies. In 25% of the surveyed organizations, funding is purely bottom-up (researchers spontaneously send projects on their own initiative), in 15% funding is purely top-down (calls for proposals on selected themes) and in the remaining 60% a combination of both is applied. The main criterion for selecting a theme or funding priority is the scientific excellence of the topic and the scientific community (90%). However, more than half of the organizations - when planning new funding priorities - also take into account 'political' or 'strategic' criteria such as improvement of national research structures (61%), strengthening national innovation (55%), and overcoming national research deficiencies (55%). When asked about funding priorities in the field of neuroscience, 88% of the surveyed organizations answered that they are funding projects with the topic 'neurodegenerative diseases', 85% 'basic neuroscience', 76% 'cognitive and behavioural neuroscience', 64% 'other neurological diseases', and 64% 'psychiatric diseases'.

(B) Concerning the funding instruments (single projects vs. networks/consortia/centres), 45% of the funding organizations apply the pure single project scheme, 3% the pure network scheme and 52% a combination of both, with high discrepancies among them concerning the respective proportions between single project and network funding.

(C) The evaluation process of submitted proposals relies in all surveyed organizations on a peer review by scientific experts, but the designation criteria for experts are variable: 2 organizations select exclusively national experts, 4 exclusively international experts and 27 opt for a mixture of both. The chance for a submitted project proposal to be selected for funding is usually quite low. In most funding organisations only about 20-30% of the applicants are positively reviewed and receive the requested grant, but this rate may even drop to 10-20% (6/33 organisations). In only five of the surveyed organisations the success rate is higher than 50%.

(D) Between the years 2002 and 2006, the summed up funding budgets for neuroscience research fluctuated between about 300 and 500 million euros per year. Not unexpectedly, there are high differences in contribution to this amount between funding organizations. In general, neuroscience research is among the well-funded research areas, and the funding volume is on average close to 20% of the whole biomedical budgets.

Dr. Patrizia Tosetti
European Commission DG Research

TITLE: "*The EC funding policy for neuroscience*"

Since the 80's, the biomedical funding at EU level has markedly increased: from 135 projects and €65 M between 1987 and 1990 to 290 projects and €483 million (M) during the framework program 5 (FP5) between 1998 and 2002 (60 dedicated to the brain). In 2000 the resulting balance is (i) that brain research is well supported at national level with good know-how and skills and (ii) strong EU research networks established as a result of past decade investment. On the other hand, several deficits emerged since (i) brain research efforts are still fragmented bringing duplication, (ii) barriers between fields and disciplines still remain, (iii) there are weak links between basic, clinical and translational research and (iv) most activities are implemented in a national framework and context.

The general European research area (ERA) organization in 2000 consists in an open coordination between national programs, FP6 (2002-2006) and European partners and should open on One European research policy. Its implementation is a combination of:
(i) Focusing efforts to support brain research projects: €2255 M Life sciences, genomics & health, info society, food safety and quality and policy research.
(ii) Structuring and management in 4 compartments: training and mobility (e.g. Marie Curie actions), infrastructures, science and society and R&D and innovation.
(iii) Strengthening of ERA thanks to networking and mutual opening-up of programmes and by coordinating R&D and innovation activities with policies at the national level.
The role of FP6 on brain research at EU level thus consists in addressing fragmentation, translating knowledge and more generally, in reinforcing global coordination which underlies the following questions: how to optimise efforts? How to identify priority areas for cooperation and synergies to ensure improvements in fighting brain diseases?

During FP6, and regarding brain and brain-related diseases, 71 projects have been supported for a value of €256 M and 900 institutions/laboratories were involved. The research areas covered by this FP were:
(i) Basic brain functions (€55 M) including learning & memory, synaptic processing, stem cells, brain development, sensory systems, cortical processing, new technologies, excitotoxicity and sleep.
(ii) Overarching (€48 M) including brain imaging, brain tissue banking, animal models, brain databasing, neuroinformatics, new diagnostics and innovative therapies.
(iii) Psychiatry (€30 M) including addiction, affective disorders, depression, autism and schizophrenia.
(iv) Neurodegeneration (€65 M) including protein aggregation, neurodegeneration, neurogenesis, early markers and new therapeutic molecules
(v) Neurology (€54 M) including ataxias, neuroimmune disorders, epilepsy, rare neurological disorders, perinatal brain damage, dyslexia, pain and stroke

As a summary, the objectives of ERA-Net NEURON are to share information about national programmes, to coordinate national initiatives in the field: Joint call published in Jan 2008 and to increase the link between Neuroscience and civil society. The successes of FP6 have been (i) a good response from the, scientific community to the proposed approach and areas tackled, (ii) a good representation of academia and industry, (iii) an involvement of many renowned leaders in the respective fields, (iii) a high visibility in scientific and lay media, with many references to the initiatives supported, (iv) a concentration on translational research (by definition highly multidisciplinary and well in line with collaborative nature of the EU programmes) and (v) a programme benefit from consensus in scientific community on the need of large interdisciplinary teams to tackle brain diseases (genetics and genomics, validation of treatments, development of new diagnostics). On the other hand several limits appeared during this FP: (i) a less well covered clinical and epidemiological research, (ii) a need to scale up Pan-European approach and (iii) a lack of "large scale resources" that build up the necessary tools and technologies, such as samples/tissue repositories and animal model network for validation of suitable models to study human diseases.

The new FP7 (2007-2013) has a total budget of €54,582 billion of which health budget is 5,984 billion. It aims at consolidate FP6 efforts by further reinforce translational research (collaborative research), research on prediction of suitability, safety and efficacy of drug and treatments (innovative medicines initiative, IMI) and at promote pan-European collaboration in brain research (ERA-Nets and joint programming). It is divided into four specific programs:
(A) Cooperation, to gain leadership in science and technology by supporting cooperation between universities, industry, research centres and public authorities across the EU and rest of the world.
(B) Ideas – European Research Council (ERC) to stimulate the creativity and excellence of European research through the funding of "frontier research" carried out by individual teams competing at European level
(C) People – Marie Curie Actions to develop and strengthen the human potential of European research through support to training, mobility and the development of European research careers
(D) Capacities to enhance research and innovation capacity throughout Europe

(A) Cooperation is divided into four sub-programs: (i) collaborative research, (ii) joint technology initiative (JTIs), (iii) coordination of non-Community research programmes and (iv) international Cooperation (INCO) applied across ten themes: health, food, agriculture and fisheries, biotechnology, nanosciences, nanotechnologies, materials and new production technologies, energy, environment (including climate change), transport (including aeronautics), socio-economic sciences and humanities, space and security. Brain research can be addressed in three pillars of EC health research which are: (1) biotechnology, generic tools and technologies for human health = diagnostics, imaging, regenerative medicine tools, (2) translating research for human and (3) optimising the delivery of health care to European citizens = public health. The pillar number 2 specifically includes the section "brain and related diseases and human development and ageing" which contain better understanding of brain function and dysfunction and thus:

- Brain function: integrated micro and macro structures and dynamics of the brain
- Brain dysfunction: neurological and psychiatric diseases
- Search for new therapies, including regenerative and restorative therapeutic approaches
- Focus on translational clinical and industrial research leading to:
    - Better diagnosis of brain diseases
    - New drugs
    - Innovative brain-machine interfaces

The FP7 first call has funded 20 (12 and 8 additional) proposals for €92 M concerning brain research of brain related research on the following themes: stroke, memory loss, neuronal coding, glia, anxiety, spinal cord repair, brain imaging, ion channel structure and vision. The FP7 second call has funded 23 (11 and 12 additional) proposals for a total of €99.5 M on the following themes: mood disorders, neurodegenerative, diseases, vision, adolescent mental, disorders, dopamine neurons, x-linked neurological disorders and neural stem cells. The topics of the third "health" call to be published in September 2008 are: synaptopathies: genesis, mechanisms and therapy, identifying genetic and environmental interactions in schizophrenia, optimising current therapeutic approaches to schizophrenia, understanding the blood brain barrier to improve drug delivery to the brain and psycho-social factors of brain disorders. A call for IMI was also published on 30 April 2008 which topic was related to brain disorders:

- Pain research: biomarkers for safer and more effective treatments
- Novel therapies in psychiatric disorders
- Neurodegenerative disorders: Bridging the preclinical / clinical divide

(B) Ideas – ERC aim is to stimulate the creativity and excellence of European research through the funding of "frontier research" carried out by individual teams competing at European level. It emerges in the FP7. The principles of the ERC are:

- It is investigator-driven research.
- It consists in individual independent teams.
- The funding is for up to 5 years.
- It addresses basic and applied research across all research fields.
- It includes Europe-wide competitive funding structure and its only criterion is excellence.

The ERC grants are:

- For young researchers (less than 8 years from award of their PhD) ERC Starting Grants.
- For senior researchers (more than 8 years after PhD) ERC Advanced Grants.

(C) People: Marie Curie actions which aim are "human resource development in R&D in Europe". It consists in:

- Initial training of researches in Marie Curie Training Networks,
- Life-long training and career development:
    - Individual Fellowships: Intra-European.
    - Co-financing of regional/national/international programmes.
- Industry-academia pathways and partnerships and Industry-Academia Knowledge-sharing Scheme (IAPP).
- International dimension:
    - Outgoing & Incoming International Fellowships.
    - International Cooperation Scheme.
    - Reintegration grants.

There are as well possibilities for brain research funding outside the Health Theme:

(i) In the ICT Work Programme:
    - The FET Programme includes Neuroinformatics, robotics and brain-machine interfaces.
    - E-Health concerns personal health systems (biosensors), patient safety and virtual physiological human.
    - E-Inclusion ICT and ageing

(ii) In the Nanosciences Work Programme as well: Nanomedicine.

(iii) In the Public Health Program in the sections:
    - Action on Dementia:
        - EURODEM: the European Community Concerted Action on the Epidemiology and Prevention of Dementia

- EUROCODE developing strategies and mechanisms for preventing, exchanging information on and responding to non-communicable disease threats, including dementia
- Actions on Autism: EU Autism Information System project
- Actions on MS: European Multiple Sclerosis Platform

Further information can be found on the following sites:
- Seventh Framework Programme: http://cordis.europa.eu/fp7/home_en.html
- Information on research programmes and projects: http://cordis.europa.eu
- IMI: http://www.imi-europe.org/Pages/default.aspx

Prof. Joel Hasse Ferreira

Portugal - EC Parliament representative (Scientific and Technological Options Assessment: STOA).

Recapitulate of the talk:

"1. Neuroscience is a very important field in the Health Policies. It has to do with the human being as a whole. In the European Parliament, mainly in the STOA Panel, (Scientific and Technological Options Assessment) we are trying to analyse more profoundly the importance of scientific research and the technological and clinical applications in the Health sector. One of our last annual lectures was about neurosciences. Concerning health, I went to Ljubljana, to speak in a Conference about the Burden of Cancer, last February, the most important event organised by the Slovenian Presidency, in the Health field. And more recently, last May, I received in Brussels, during one week, the Professor Simon Poldnar, Chairman of the Neurosciences Society of Slovenia. And I will visit him in Ljubljana, in a few weeks, to follow what is being done there by him and other researchers. And it is also important to underline that it is a field where the support for research is very important. The public powers should create or improve the conditions that will contribute to the best work or the scientists and researchers. And this field of Neuroscience, I think it should clearly be a priority. Even yesterday, in Strasbourg, in the Plenary of the European Parliament, the French President Nicolas Sarkozy, speaking as President of the European Council, the first reference he made about Health has been about Alzheimer's disease.

2. Concerning the Financing and Funding on Neuroscience Research and about Research in general, I must mention that in the discussion of the Financial Perspectives for 2007/2013, it was approved that the spending with Common Agricultural Policy will be gradually reduced and the financing for research and environment should increase gradually, during all these years. One difficulty could then be the distribution of money to the different kinds of project researches. The other problem could be the resistance of farmers and some politicians to reduce now the support for the food production, in this circumstances that we are facing now.

3. Anyway, in the 7th Framework Program for Health, there is a clear mention in the 2.2.1- "Brain and brain related diseases". And the mention of the relevant "age related illness (as dementia and Parkinson's disease) "is very important because of the threat these diseases represents for many citizens and their families. But also references to the "childhood and adolescent mental disorder" are relevant. It concerns the future of the humanity. According to the available data, the research in neurosciences had a positive evolution from the 4th through the 5th and the 6th Framework Program.

4. We must take into account the changes in the NEURO-ERA-NET that may happen probably with the new Framework Program. We hope that the changes will not cause any problem in the financing of the research projects involved. On the contrary, I expect that the management system of research funding will improve, as a whole.

5. It is very important to finance the scientific research, but it is also very important to give support to the applied innovation, concerning the equipments, the diagnosis and the clinical research activities. And now, especially during financial and economic crisis, many States are not able to finance strongly the research. Today the financial restrictions are relevant and some difficulties could apply to scientific research in the Universities and in State Laboratories, even on the financing of private research in this field. We must deal with these restrictions in a very creative way.

6. Another point to take into account is the difference of the schedule for the Political Budgets and the Scientific Research needs. In this case, the Financial Perspectives being for the period of 2007-2013, could be a real progress in this need of harmonisation. And the review and the possible evolution of the Financial Perspectives in 2010 can give us (neuroscientists and MEPS) a special opportunity to increase the amount to the research in neurosciences and not only in some fields which are more or less in "fashion".

7. We also must take into account the possibility of getting finance from private organisations, foundations or international societies. But in these cases, the scientists should be aware of some dangers. Not only on how to do the research but also when publishing the results. Some laboratories, Equipment and Drug companies have their own interests and would like to influence, if they can, some studies and research projects. Only very few scientists which doesn't deserve this name could be influenced. Also, the great majority of the companies are very interested in the progress of Science in this field and they support research projects with those objectives as well. Of course, I believe that this situation doesn't occur in neurosciences and I think that the scientists and researchers in neurosciences are absolutely rigorous in their work. Anyway, it is a question that the scientific community can solve. That's one the reasons why the peer review is very important.

Before concluding, I would like to remark the importance of increasing the funds for research in neurosciences. I expect that this symposium on "Frontiers in Neuroscience and Project for their funding in

Europe" will give a very positive contribution for a better and more effective funding with public and private resources.

Anyway, after this Conference, I will speak to my colleagues in the Parliament mainly from the STOA Panel and Budget Committee, with President Barroso's office with some members of the European Council, to share my views on what had been discussed in this Symposium and to reinforce the importance of financing the research in neurosciences."

Prof. Richard Nakamura

USA - NIH.

TITLE: "*The Funding policy for Neuroscience in North America*"

Overall funding goals of the NIH are:
- Generate the best research
- For overall scientific knowledge
- For the public health to reduce the burden of disease

The first observation concerns the daily disease burden by Illness in the entire world and for all ages in 2000. It shows that unipolar depressive disorders are the fourth cause of disease behind lower respiratory infections, perinatal bad conditions and HIV/AIDS. When focusing on the 15-44 years old the total impact of mental illnesses (including unipolar depressive disorders, alcohol use disorders, self inflicted injuries, schizophrenia and bipolar affective disorders as well) is the first cause of disease and when focusing on the same age range in United States, Canada and Western Europe, the unipolar depressive disorders appears to be the major cause of illness. The NIH has of course to take these observations into account to organize its policies and Neuroscience appears as a major field to fund and to promote (Information at: www.nimh.nih.gov).

The NIH is structured with an "Office of the Director" at the top. This office manages numerous specialized institutes like for example: National Institute of Mental Health. The 2007 NIH discretionary budget authority allows $29.228 billion. 52.7% is dedicated to research grant projects, 9.6% to intramural research, 9.7% to R&D contracts, 9.9% to research centres and the remaining 18.1% dedicated to research management, other research and training. The NIH Neuroscience budget is around $5 billion but there are other US supports from national science foundation (NSF), department of defense (DOD), department of energy (DOE) and non federal from private non-profit and for-profit organizations (pharmaceuticals and biotechnologies). The NIH contribution to Neuroscience is itself subdivided into several national institutes like for example the *National Institute* of Neurological Disorders and Stroke (NINDS).

The NIH policy relies on the following principles (80% of NIH money invested in such awards):
- Open competition for grants.
- Project based.
- Peer review for scientific quality (scientific board mostly composed of national experts).
- Institute funding decision.
- Funding for up to 5 years.
- Most applications not solicited.

Besides NIH fostering are awarded in accordance with the following key points:
- Pick well trained and brilliant, young scientists.
- Support ideas and PIs, not projects.
- Retrospective review works best.
- Review with outstanding expert reviewers.
- Ensure the reviews have impact but afterwards provide scientific freedom.
- Allow risk taking, allow failure and field changing as well (sabbaticals possible also).
- Provide salary security.
- Minimize impediments/red tape and finally solve the problem of renewal.

The review process for an NIH research grant starts with the application submission and thus primarily relies on bottom-up scheme (a scientific team initiates a research idea and builds a project). Spontaneous submitted applications are sent to a centre for scientific review (CSR) (A) where they are assigned to the appropriate study section (B). Their scientific merit is thus evaluated and an institute evaluates then the program relevance. The application is sent the advisory council and boards which will recommend the action and finally, the decision is transmitted to the Institute director who will take the final action for NIH director and allocate funds or not.

(A) The CSR serves as central receipt point for PHS Grant Applications. It assigns applications to CSR Integrated Review Groups/Study Sections or Institute Scientific Review Groups. It also assigns applications to NIH Institute(s) as potential funding component(s) and conducts initial scientific merit review of most research applications submitted to the NIH in more than 100 Study Sections.

(B) The study sections (for the scientific review) are managed by a Scientific Review Administrator (SRA) who is a professional, usually at the Ph.D. level and whose scientific background is close to the expertise of the study section. Each standing study section has 12-24 members who are primarily from academia. About 60-100 applications are reviewed at each study section meeting.

The review criteria for the projects are the following:

- Significance: Does the study address an important problem? How will scientific knowledge be advanced?
- Approach: Are design and methods well-developed and appropriate? Are problem areas addressed?
- Innovation: Are there novel concepts or approaches? Are the aims original and innovative?
- Investigator: Is the investigator appropriately trained?
- Environment: Does the scientific environment contribute to the probability of success? Are there unique features of the scientific environment?

Three trends have been studied from 1995 to 2006 (FY) for NIH competing research project grants (RPG) applications: reviewed applications (RA), awarded applications (AA) and success rate (SR). RA has constantly increased and markedly during the "Doubling period" (FY 1998–2003) and has continued; whereas AA decreased from 2004 to 2006. The number of applications for competing awards increased. The drop in the number of AA since then has resulted in lower SR. The average size of competing R01 equivalent awards has continuously increased from 1998 but stagnates around $365,000 since 2005 (*R01 Equivalent Awards are the largest investigator initiated activity of NIH. They are normally defined as R01, R29 and R37. R23 was part of the definition until the activity was discontinued, in the mid 1980's*).

The peer-reviewing system at the NIH is one of its cornerstones. Indeed, increasing breadth, complexity and interdisciplinary nature of biomedical science are creating new challenges for peer review. Besides, funding trends aggravate the stress on peer review. The NIH Response is thus: reviewing – and enhancing – peer review system. The NIH reviewing system continuing charge is to "Fund the best science, by the best scientists, with the least administrative burden..." but recognize that "best" is dependent on many factors including: scientific quality; public health impact; mission of Institute or Centre; existing NIH portfolio. The reviewing core priorities are therefore:

(1) To engage the best reviewers since the excellence of peer review is directly correlated to our ability to recruit and retain the most accomplished, broad-thinking and creative scientists to serve on study sections.

(2) To improve the quality and transparency of reviews. Indeed, peer review must consistently identify an application's relative merit, potential for scientific and/or public health impact, and feasibility. Indeed, the reliability of individual rating scales is a monotonically increasing function of the number of steps. As the number of scale steps increases from 2 to 20, the increase in reliability is very rapid at first, but tends to level off at about 7. A seven scale steps provides appropriate balance between scale reliability and discriminative demand on the respondent (Nunnally, 1978). Several goals have been planned to achieve this among which:
- A modification of the rating system to focus on specific review criteria, with less emphasis on methodological details and more emphasis on potential scientific impact.
- A shorten and redesign of applications to align with the NIH review criteria starting with R01, R15, R21, R03, K, and F applications.

(3) To ensure balanced and fair reviews across scientific fields and scientific career stages and reduce burden on applicants. Peer review should fairly evaluate proposals from all scientists, regardless of their career stage or discipline, and avoid bias towards more conservative and proven approaches at the expense of innovation and originality:
- It should not disadvantage early stage investigators.
- It should apply the appropriate weighting of past performance and future potential for impact as a function of career stage and productivity.
- It should be designed to minimize the need for repeated or multiple applications from meritorious scientists to achieve funding support.
- It should encourage "transformative" research.
The average age of NIH RPG Investigators since the 1980 has increased from 37.2 to 42.2 years. To overcome this trend several goal have been planned among which:
- Encourage and expand upon the Pioneer, EUREKA and New Innovator awards review experience to encourage risk taking by applicants:
    - Applicants propose ideas with "transformative" potential as main criterion in concert with a prospective evaluation to measure effectiveness of this approach
    - Continue to grow the Transformative Research portfolio to reach to ~1% of R01-like awards
- Based on analysis of success rates as a function of initial scores, reduce the need for resubmissions

(4) To develop a permanent process for continuous review of peer review. The NIH peer review process should commit itself to a continuous quality control and improvement process based on a more rigorous and independent prospective evaluation that favours rather than discourages adaptive and innovative approaches to review and program management:
- Pilot and evaluate new models of review
    - 2 stage reviews (editorial board models)
    - The use of "prebuttals" (jargon for pre-emptive rebuttal)
- Pilot and evaluate different methods for ranking relative merit of applications
- Pilot and evaluate high bandwidth electronic review
- Develop metrics for monitoring performance of review

The Key objectives for the future are:
- Develop a science of science.
- Develop measures to evaluate progress.
- Pay more attention on the problem of ethics, social implications and conflicts of interest.
- Need international comparisons, not just internal US evaluations.
- Need international collaboration and cooperation to achieve truly universal progress towards world public health.

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ERA-Net NEURON
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