Scientific Workshop

~Future Developments in Neuroscience~

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Report by

Bérangère Ballion

Foreword by

François Bourre and Bernard Bioulac

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The Workshop was introduced by a word from the NEURON Coordinator Dr. Marlies Dorlöchter in order to explain the ERA-Net NEURON Scheme and the scope of the Workshop.
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FOREWORD

This workshop entitled « Future Developments in Neurosciences » was organised to highlight the future scientific and medical challenges in neurosciences and to pinpoint the scientific ways which will be powerful to take up them. Neurological, psychiatric and others central nervous system (CNS) diseases have a higher and higher social and economic impact. It is therefore highly important to cover the range of biological concepts and technologies which will be helpful to understand normal and pathological biologic processes and thereby to develop new therapies to treat CNS diseases. So, the speakers focused their conferences not on a specific disease but on more general biological or technological fields.

Pr. Jim Van Os gave talk on "*Gene Environment Interactions in Psychiatric Diseases*" schizophrenia and related psychotic disorders being present in all social cultures and historical periods but becoming an emergent problem of public health. At the European level a very large project was launched to examine the role of genes and different environments. Indeed the main question is why in some individuals expression of psychological vulnerability never progress to overt illness whereas in some others psychotic diseases will manifest in clinical expression. The project is therefore focus on person-environment and gene-environment interactions to understand which factors are involved and more particularly the epigenetic mechanisms controlling gene expression.

Pr. Alain Prochiantz focused his presentation on "*Neurodevelopment at the Cellular and Molecular Level*" and how the cells participate in the construction of the CNS not only for its anatomy but also for its functionality. Developmental errors during embryonic or even adult life are certainly responsible for CNS diseases. Thus, knowledge of embryogenesis mechanisms is a keystone for futures therapies. CNS formation and functionality are depending upon cell differenciation which is itself under the control of gene regulation. Epigenetic mechanisms are one of these regulating mechanisms. Thus, analysing and understanding epigenetic mechanisms will be crucial for developing novel views on many diseases as well for defining new therapies or to provide grafting materials.

Pr. Richard Frackowiak gave a talk on "*Brain Neuroimaging for Disease and Cognition*" and pointed out the difficulties to collect data and to design experiments in brain imaging. Whereas in the past years anatomical correlations and temporal characteristics were analysed, since ten years most scientists focused on functional integration. A radical change in approach is to move away from the group studies to single subject studies with single scan analysis which requires high computer capabilities and data storage capacity. Another part concerned the multimodal and multivariable approaches and particularly the functional and structural connectivity between cortical areas and subcortical structures and the inherent comprehensive map of neural connections (connectome) and the very new mathematical approaches. These approaches will allow to move to population samples to generalisable inferences and to move towards individual patient prognosis and diagnostic.

Dr. Viktor Jirsa gave a talk on *"Multi-scale Brain Dynamics in the Computational Neurosciences"* in which he explained an ambitious project aiming to merge structures and functions by performing network simulation in a virtual brain. Indeed isolated studies cannot answer to the question of how the brain works and how there is established a hierarchy of integration levels in the central nervous system. To traverse the different levels of organization (genes, molecules, synapses and all the ways of the systems), multiscale dynamics is used to develop a virtual brain able with the same dynamic and network as a human brain. This will be a powerful tool for knowledge and understanding brain network but also as a predictive tool.

Dr. Martin Dichgans focused his conference on "*Challenges and Opportunities on Stroke Research*". Indeed stroke is the leading cause of physical disability, the second most frequent cause of dementia and the third cause of death in Europe. Silent brain infarcts are associated with many cases of cognitive impairment and are often caused by cerebral small vessel disease (CSVD). Although little is known about CSVD many research areas are under investigation and could be very informative. Particularly identification of mendelian variants, developments of cellular models, hemodynamic studies, clinical trials, identification of new therapeutic targets are needed to improve diagnostic and treatment of stroke.

This workshop depicted future challenges in basic neurosciences but also in neuroimaging and computational neurosciences. The last talk focused on stroke showed clearly that these challenges could be powerful in this pathology. Thinking about neurological and psychiatric diseases and other disorders, it is obvious that fostering developments of these new tools and concepts will be of great interest for diagnostics and treatments.

Future developments in neurosciences

Jim Van Os

Maastricht University, Maastricht, The Netherlands.

TITLE: *"Gene environment interactions in psychiatric diseases".*

Schizophrenia and related-psychotic disorders are wide-spread psychiatric disorders described in all social cultures and historical periods. Their prevalence is high in young people comparing to somatic disorders which appear later with age. They come along with cognitive disorders, social and behavioral dysfunctions and thus are an emergent problem of public health.
For this purpose, researchers in the EU established a large-scale project, the EU-GEI (European network of national schizophrenia networks studying gene-environment interactions) by examining the role that genes and different environments play on these mental disorders and more specifically on the schizophrenia risk. Today, the international project involves more than 7,500 patients and their families from 15 countries and aims to define a roadmap in mental health research to:
(1) Improve treatment and social participation by defining the best treatment given,
(2) Understand expression and life course trajectories,
(3) Consider the public health impact and implications,
(4) Determine the causes and mechanisms.

The first question concerns interactions between the person and the environment. Indeed, the brain is context-sensitive and by compiling the environmental sensory inputs (facts) and the cortical processings (expectations), it built affective social world representations leading motivation and interactions. In this context, multi-dimensional psychiatric syndromes can be understood as an imbalance in the cycle of adaptation to the social context. By affecting the health, the status syndrome is an example of this imbalance of adaptation to the social context. Indeed, a large study including 20 rich nations and USA shows that income inequality tend to have lower life expectancy, higher infant mortality, more mental illness, more obesity, more murder, less trust, and less upward mobility.
Nature and nurture could they explain this imbalance of adaptation to the social context?
In case of schizophrenia, the heritability (proportion of phenotypic variation in a population that is attributable to genetic variation among individuals) is about 80%. In identical twin (100% genetically identical), if one member is affected by schizophrenia, the schizophrenia risk for the co-twin is 50%. This risk is less (about 15%) in fraternal twins (50% genetically identical)

In fact, genes mediate environmental sensitivity meaning that genetic variations induce sensitivity to environmental causal risk factor and thus possible psychosis-related cerebral outcome.
During the childhood, the brain development is sensitive to environment and sensory informations (sound, touch, vision, smell, proprioception and tast). The development can be affected by gene expression level which could be modified by epigenetic mechanisms (changes in the underlying DNA sequence such methyl groups which can tag DNA and activate or repress genes) affected by several factors such environment.

A link between European environment and severe mental illness is now established. Indeed studies concerning the health of the migrant populations, the built environment, or developmental trauma show that relative risk severe mental illness could be increased from two to five-fold. For example, children growing up in big cities have more than two-fold risk of developing a mental disorder compared to children in rural environments. Immigrant populations have much higher risk of developing disorders compared to the risk in both the host country and the country of origin.

These factors (trauma, migrations, urbanicity) can lead schizophrenic disorders linked to a social defeat feeling which is consequent to chronic experience of marginalisation, subordination or exclusion. Also, cannabis use increases the relative risk of severe mental illness per 2. The research for a statistical interaction between environment and genes in the mental illness seems to show a close relationship between genotypic variations, environments (urbanicity, cannabis use…) and the increase of related-risk of mental illness (schizophrenia, psychotic disorders, reduction in cortical thickness…).

Concerning the brain development, a window of environmental exposure during the development of the human brain shows for example that postnatal exposure to cannabis, trauma, urban upbringing or ethnic minority are detrimental to functional abilities in neurocognition, affect, and social cognition.
In terms of neurobiology, neural circuits could be relevant in psychotic disorder including a specific circuit-integrating bottom-up sensory input with top-down cognitive control which can become sensitized after repeated environmental exposures. In case of schizophrenia, there are interactions between phenotypes of psychotic disorder, altered regulation of dopamine neurotransmission in the brain, and environmental exposures. For example, exposure to childhood trauma induces functional or structural alterations of connections prefrontal cortex- nucleus accumbens, nucleus accumbens-ventral pallidum, amygdale-hippocampus, VTA-nucleus accumbens. The nucleus accumbens is considered as the site of integration of bottom-up sensory experiences with top-down cognitive control of dopamine neurotransmission. The repeated exposure to environmental factors could dysregulated the balance between, on the one hand, activation of the nucleus accumbens from hippocampal and amygdala projections and, on the other hand, inhibitory control of the nucleus accumbens by glutamatergic projections from the prefrontal cortex. The resulting enhancement of bottom-up sensory experiences without appropriate top-down cognitive control is proposed to underlie aberrant representations of the social world. Studies have shown expression and trajectories of mental illness based on extended phenotype of general population with a behavioural expression vulnerability around 20%. In this context, the environmental impact and the developmental impairment can lead to psychosis and affective depress (help seeking or social conflict) and negative and cognitive affects (reduced social competence), respectively. From there and based on the clinical phenotype, the mental disorder prevalence is about 3%. In summary, the roadmap mental health research lead to improve treatment and social participation, understand expression and life course trajectories, public health impact & implications and study causes and mechanisms.
The project is designed to focus on the effects of person-environment and gene-environment interactions on brain pathways and psychological vulnerability, and to elucidate how subtle, but measurable behavioural expressions of vulnerability for psychotic disorder are mediated by cerebral and psychological pathways. Follow-up research in the project is expected to establish why, in some individuals, expression of vulnerability will never progress to overt illness, while in others, schizophrenia will manifest in clinical expression.

Alain Prochiantz

Collège de France, Paris, France

TITLE: *"Why studying development is important to understand hidden aspects of brain physiopathology".*

During a long time, cellular biology remained margin in the understanding of the central nervous system. Nevertheless, it is necessary to consider the cellular and molecular level in the neuro-development, and how cells participate in the construction of organs such as the brain. Therefore, neuroscientists have to know how neural cells participate to the cellular organization. For example, cell polarity is certainly a key in organ organisation, not only for its anatomy, but also considering the functionality of such an organ. In addition, the brain undergoes silent embryogenesis mechanisms allowing a constant and adaptive renewal. It is then possible and even certain that some diseases are the resultant of developmental errors during embryonic phase or during the adult life. We know that mechanisms supporting development are under genetic and epigenetic control. Waddington in 1940 proposed a concept of landscape epigenetic (picture on the genetic regulation of the development) according to which the stability of the wild phenotype would be due to the genome capacity of buffering environment variations and the genetic inheritance. Since this time, many publications have reported that gene regulation by epigenetic are really a keystone in landscape of biology and more specifically in the regulation of cell differentiation and morphogenesis.
Some genes can selectively modulate phenotype in vertebrate development such HSP90 considered as a capacitor for morphological evolution. Rutherford and Lindquist have shown that, in normal conditions, Drosophila HSP90 buffers numerous cryptic variants which can be expressed when exogenous conditions, like temperature, are changing inducing an HSP90 misfunction. Architecture of the brain is an essential factor for a full functionality of the central nervous system. In a same manner Otx and Emx homeobox genes are clearly involved in brain development. These genes code for four transcription factors, coordinated pattern and expression timing being a key for development of brain and forebrain. Indeed during early stages of brain development, both expression pattern, for example a gradient of Otx2 protein can be observed with a maximum in the anterior neuroectoderm of the headfold and a gradually decreased expression in the more posterior ectoderm, and timing, Otx2 being expressed very early, Otx1 and Emx2 expression can be detected just after and the expression of Emx1 arriving latter. This coordinate expression of these genes in term of timing and location is a necessity to build a functional central nervous system. Moreover Brodski and collaborators (2003), using different knock-out mice, have shown that protein Otx2, was involved not only into this architecture but also in brain functioning. Indeed in Otx2 KO mice and accordingly the Midbrain-Hindbrain Organiser (MHO) are shifted caudaly, the midbrain dopaminergic neuronal population expands ectopically whereas the extension of the hindbrain serotonergic cell group is decreased. Moreover in mutants in which Otx2 and the MHO are shifted rostrally, dopaminergic and sertotonegic neurons are relocated at the newly positioned MHO. In these latter knockout mice, a higher locomotor acitivity was observed. These results suggest that the position of the MHO during embryogenesis can modulate adult locomotor activity.
This developmental genetic concept leads to understand the role of the "niche" in the epigenic fixation, in the maintenance and in the regeneration. Wang and collaborators (2009) have shown that three Rs of Hox gene expressions were involved in regeneration, repair and remembering identity of hung and foot fibroblast. Hox genes encode transcription factors that specify embryonic positional identity in cells and guide tissue differentiation. Moreover, expression of these genes is dependent upon epigenetic mechanisms ensuring modulation of expression in adult. This involves the interplay of histone methylation, demethylation and intergenic transcription of long non-coding RNAs. In a same way, Yakushiji and collaborators (2009) proposed an amphibian model for study genetic and epigenetic control of organ limb regeneration.
All these studies lead to understand the lineage stability or plasticity through the epigenetic inheritance and its modifications.This will allow 1) understanding the physiological function of cell turnover in the adult brain and (2) developing novel views on several pathologies (depression, schizophrenia, brain tumors...). Finally, because pluripotent stem cells are able to form all the body's cell lineages, human iPSCs studies and specifically reprogramming cellular strategies (induced pluripotent stem cells) will (1) allow to develop experimental models for human diseases and identification of therapeutic targets and (2) may provide a source of grafting material. The reprogramming strategies using viral transgenes encoding the transcriptional factors used in deriving hiPSCs and leading genetic modifications have been performed by Saha and Jaenisch (2009) but many questions are not resolved yet, particularly the epigenetic stability of differentiated cells, factors allowing that remaining largely unknown.

In occurrence of neurological diseases (some ataxia, apraxia, trichothiodystrophy…), deficiencies of DNA repair can be implicated inducing mutations or cellular apoptosis due to DNA lesions induced by oxidative stress (during proliferation or differentiation) or transcriptional interference. Indeed imbalance in mitochondria energetic metabolism is able to induce such a mechanism in all organs including brain. These failures in DNA repair leading to neurodegenerative diseases have been shown in thalamus neurons (Brasnjevic and collaborators, 2008). In consequence, DNA damage response (DDR) could play a major role in the neuronal development, organization and maintenance (Barzilai and collaborators, 2008).

Instability of the genome (i.e. changes in chromatine structure, regulation of gene expression, gene mutations, new gene formation, chromosome rearrangements) epigenetic modifications and incidence of environment can lead to phenotypic modifications, population adaptation and speciation, and finally to an evolutionary neurogenesis. This "noval" neurogenesis includes the jumping-gene roulette theory which making copies of themselves and providing stochastic process for generating brain diversity (Martin, 2009). The dogma that the adult brain has no capacity for generating new neurons is now obsolete but the functions of the adult neurogenesis are largely unknown. Deng and collaborators addressed the question of this adult neurogenesis regarding memory and learning. The hippocampus, a crucial structure for episodic and spatial emotion, is also implicated in emotional behavior through its interactions with brain structures. Does the integration of new neurons into the adult hippocampal circuit influence hippocampus-related behavior? At this time no clear answer can be proposed. Against, our knowledge of the functions of hippocampal neurogenesis has considerably advanced. In particular considering a major brain function such memory, how news neurons could affect learning and memory in adult organism. Deng and collaborators (2010) display a study questioning the physiological functions of adult neurogenesis in memory and erasing memory and links with pathologies such as schizophrenia or depression. Indeed, previous studies showed stimulated effects of antidepressant drugs on adult hippocampal neurogenesis (Sahai and Hen, 2007) and regulation of disrupted-in schizophrenia 1 in integration of newly adult generated neurons (Duan and collaborators, 2007).

Concerning injury-induced membrane repair, it has been shown several emergency mechanisms such as nucleation, oxidation, vesicule translocation and membrane resealing.

During the development, it has been shown critical periods. Some psychiatric neurological disorders occurrence may be linked with emergence of adolescence such impulse control disorder, substance use disorder, schyzophrenia etc (Paus and collaborators, 2008). In rodents, implementation of binocular vision seems to be critical one month after birth. Nevertheless, by reopening a period of plasticity, neurodevelopmental disorders can be reversed in adult. At this time we don't know exactly how to reopen such a period but identification of the molecular keys allowing plasticity should be a priority in the next years.

In conclusion, studies consider actually incidence of development in implementation of pathological disorders. But it remains important to bring supplementary data concerning developmental genes throughout life, their regulation, epigenetic , DNA repair, membrane repair, adult cell renewal, lessons from non-mammals (fishes, frogs, amphibians), brain metabolism, critical periods and reopening plasticity and basic aspects of cell biology (signal transduction, sub-cellular compartmentalization etc…).

Richard Frackowiack

UNIL-CHUV, Lausanne, Switzerland.

TITLE: *"Brain neuroimaging for disease and cognition".*

The brain imaging raises nowadays major scientific interest and integrates different technological fields. The main question is how to do experiments and collect data with neuroimaging technics. Historically, function specialization bases was done in the 80's with electrophysiological recordings in the monkey to look for (1) anatomical correlations and (2) temporal characteristic changes in human brain at the microscopic level and particularly the spike discharge with a millisecond time resolution at the cell level. During the last ten years, most neuroscientists focused on motion functional integration back to the network, one of the most interesting temporal characteristics. Functional specialization in the primate brain has reached a degree of sophistication with the anatomical and physiological characterisation of human and monkey visual cortex using neuroimaging BOLD (Blood Oxygen Level Dependent) signal and neuron activity. Moreover, the neuroimaging has shown that picture presentation on TV screen and the same picture imagined by the subject activate the same functional specialized area. Past study of psychology (Kleinschmidt A. and al., Proc. R. Soc. Lond. B ; 1998) used bistable perception concept in which looking at ambiguous figures results in rivalry with spontaneous alternation between two percepts such the vase-profile illusion introduced into psychology by E.Rubin and the "my wife and mother-in-law" illusion by R. W. Leeper and E. G. Boring. Using event-related functional magnetic resonance imaging, this experimental work localized transient human brain activity changes and defined the neural correlates of flips in visual perception. During the trials, subjects had to repetitively report their conscious experience of the visual scene by key-presses, defining the occurrence of perceptual reversals and the presence of stable percepts generating the real-time sequence of perceptual fluctuations. During perceptual reversals, some regions (prestriate visual cortical areas, bilateral ventral occipital cortex and posterior intraparietal cortex, as well as in other occipital and some frontal areas) transiently increase activity but not sensorimotor cortices. Moreover, transient de-activations associated with perceptual reversals compared to stable percepts in several structures occured in calcarine cortex and the posterior thalamus. BOLD neuroimaging is also classically used in experimental working memory tasks during action-selection processes to understand the characterising functional dynamics and more particularly differential activation/deactivation of brain areas for correct and error trials. Now a radical change in approach occurs and the first shift is to move away from the group studies to single subject studies with single scan analysis which requires high computer capabilities and data storage capacity. All these changes allow bringing translation to medicine. One example concerns the perception of edge orientation: indeed, a clinical study investigated whether this fundamental visual feature and more specifically the orientation selectivity in visual cortex can be decoded from human brain activity measured with functional magnetic resonance imaging (fMRI) (Kamitani and Tong, Nat. Neurosc., 2005). Results demonstrated that fMRI activity patterns in early visual areas, including primary visual cortex (V1), contain detailed orientation information that can reliably predict subjective perception. This study is based on ideas of population coding and multi-voxel (volumetric pixel) pattern analysis of fMRI data to demonstrate neural decoding of perceived orientations because single voxel analysis and averaging over region are less informative. Moreover, humans can experience after effects from oriented and unconscious stimuli suggesting that such stimuli receive cortical processing. fMRI has been used to obtain a direct measure of orientation-selective processing in V1 and to determine the physiological substrate of such effects in visual cortex. Data showed that many parts of V1 present subtle but reproducible biases to oriented stimuli and this information could accumulate across the whole of V1 using multivariate pattern recognition and could predict which one of two oriented stimuli a participant was viewing, even for invisible stimuli (Hayes and Rees, Nat. Neurosc., 2005).

Another study was interesting in the prediction of the rapid stream of conscious experience from brain activity alone in human visual cortex. Using binocular rivalry to induce frequent spontaneous and stochastic changes in conscious experience without any corresponding changes in sensory stimulation, brain activity was measured with fMRI. Results showed prediction in primary visual cortex primarily reflected eye-based signals, whereas prediction in higher areas reflected the color of the percept. Furthermore, accurate prediction during binocular rivalry could be established with signals recorded during stable monocular viewing, showing that prediction generalized across viewing conditions and did not require or rely on motor responses. It is therefore possible to predict the dynamically changing time course of subjective experience with only brain activity (Hayes and Rees, Curr. Bio., 2005). Concerning the brain decoding and specifically representations of faces and objects in ventral temporal cortex (VTC), activity measures by fMRI showed a distinct pattern of response for each stimulus category (view of faces, cats, five categories of man-made objects, and nonsense pictures). The distinctiveness of the response to a given category was not due onlyto the regions that responded maximally to that category. Patterns of response that discriminated among all categories were found

even within cortical regions responded maximally to only one category. These results indicate that the representations of faces and objects in ventral temporal cortex are widely distributed and overlapping (Haxby et al., Science, 2001). Another example of brain decoding can be found in literature (Kamitani and Tong, Nat. Neurosc., 2005; Miyawaki et al., Neuron, 2008).

The last part concerned the multimodal and multivariable approaches considering (1) the functional and structural connectivity between cortical areas and subcortical structures and the inherent comprehensive map of neural connections (connectome), (2 the very news mathematical approaches with classification and Bayesian approaches, (3) the pathologies and the transcranial magnetic stimulation (TMS) to show causality and finally (4) the network temporal properties like synchronisation. For example, study coupling DTI (diffusion tensor imaging, a magnetic resonance imaging technique, probing the random thermal motion of water molecules in tissue) and FMT (fast marching tractography) showed partial bilateral reconstruction leading anatomical connectivity between different subcortical areas and cortical areas revealing the cortico-striato-pallido-thalamic (long loops) and cortico-striato-thalamic (short loops) connections. In another study, series of quantitative structural and functional imaging analyses were performed in patients with five distinct neurodegenerative syndromes and healthy control groups. This clinical imaging study allowed building disorder general map with functional correlation and structural covariance which showed that syndrome-associated regional degeneration patterns reflect distinct human neural network architectures (Seeley et al., Neuron 2009).
So by using contrasts and comparisons, science allows to move to population samples to generalisable inferences. In parallel, by post-mortem validation and classification, medicine allows to move towards individual patient prognosis and diagnostic.

Viktor Jirsa

CNRS, Université de la Méditerranée, Marseille, France

TITLE: *"Multi-scale Brain Dynamics in the Computational Neurosciences".*

The aim of this ambitious project is to merge structures and functions by performing network simulation in a virtual brain. Because of (1) explosion of brain imaging technology (new access to human mental function), (2) the nowadays high performance of computational hard-wares and (3) the need of an integrative platform to merge experimental datas, building a virtual brain becomes a necessity to perform a research in neural network dynamics and address fundamental questions relevant to cognition and movement. Combining informatics (data treatment), mathematical tools and clinics are to be relevant to study in multiscale way the foundations of neural information processing on various levels of organization (i.e. from cell to human behaviour) and to transfer to medical applications.

Isolated studies cannot answer the question of how the brain works and there is a hierarchy of integration levels in the central nervous system (CNS). To traverse these different levels of organization (genes, molecules, synapses and all the ways of the systems), we use the multiscale dynamics. In this context, the major question is how to get to from one level of organization (single neurons for example) to another level (neural population dynamics from example). Nowadays, neurons are considered as actors in a population, which is analyzed with statistical approaches such as mean field theory. However, this approach is often not sufficient because it assumes that neurons in a population are identical in a statistical sense. Hence there is a clear need to develop better population models that address the nature of population dynamics more realistically. Another concern is the huge amount of data available. To pass through the data, various scientific projects have emerged to overcome this weakness. Among them is « DAISY », a neuroinformatic project for the modelling of the architecture of the neocortex based on anatomy and physiology. The project includes six laboratories in Europe and Israel and is funded by the EU IST Future and Emerging Technologies program (http://daisy.ini.unizh.ch). Using detailed simulation approaches, the Blue Brain Project founded by the Brain and Mind Institute of the École Polytechnique Fédérale de Lausanne (Switzerland) investigates the brain's architectural and functional elements in an attempt to create a synthetic brain by reverse-engineering the mammalian brain from the molecular level. And finally, the European FACETS and its follow-up BrainScaleS projects aim to create a theoretical and experimental foundation for the realisation of novel computing paradigms, which maybe hardware coded in future applications (neuromorphic computation). Interaction and scientific exchange between biological experiments, computer modelling and hardware emulations provide an insight into the computing principles of the brain. The FACETS project started on the level of spiking neurons to built population models, whereas BrainScaleS aims at developing mesoscopic systems of coupled populations.

The final dimension of traversing scales of organization is the large-scale brain dynamics and behavior. This aspect is studied by the Brain Network Recovery Group (BrainNRG.org), an international consortium including 6 countries (Canada, USA, Australia, UK, Germany and France) and 17 Principal Investigators spanning the domains of computational, cognitive and clinical neuroscience. Their declared goal is the understanding of brain network dynamics in both normal and pathological conditions as it is determined through the interplay between structure and function during recovery from damage. The Brain NRG differentiates itself from the other mentioned projects by the emphasis of the macroscopic scale of organization. Though the traverse of multiple scales is certainly important here also, this group aims at exploring the capacity of manipulations of connectivity as a tool of influencing large-scale brain dynamics. The understanding of the large-scale brain dynamics is important because (1) higher integrative functions are performed by the brain network rather than individual areas and (2) many brain diseases involve a network component; bluntly put, the fact that epilepsy is a network disease/disorder does not mean that the others are not. A recent explicit example is found in the resting cell activity in the brain (for review, see Deco and al., 2011 Nat Rev Neurosci.).

The major goal of the field "brain connectivity" is to add biologically realistic connectivity to the study of brain networks. For example, the cocomac.org database represents the first database of neuroanatomical and physiological brain connectivity of the macaque. This resource allowed the construction of the first generation of virtual brains. Macaque connectivity was mapped onto the human brain considering the differential distribution of the fiber lengths and the time delays of propagation from one area to another. In conjunction, this information defines the space-time structure of couplings of the human brain (Ghosh et al. PLos CB 2008; Deco et al., Nat Rev Neurosci 2011).

In summary, to develop a virtual brain leading to network interactions and large-scale brain dynamics, researchers merge biologically realistic structural and functional information from neuroimaging with mathematical models. When built, the virtual brain is able (1) to produce the same dynamics as a human brain, which grows old, gets damaged or diseased and (2) will try to recover. One major question, naturally, is if the virtual brain can act as template for a single person, or if an individual

brain can indeed become the virtual brain? Future steps will allow to refine the implementation of the virtual brain in terms of (1) tracking and facilitating recovery (predictive models; for a given person, what are the best pathway manipulations to facilitate recovery?), (2) developing a virtual brain platform (integrate genetic, structural and functional data; identify responders and non-responders; test new strategies for recovery) and (3) increasing funding & collaboration (enhance informatics capacity; enhance mathematical sophistication; broaden clinical impact).

Martin Dichgans

Ludwig-Maximilians University, Munich, Germany.

TITLE: *"Stroke research: challenges and opportunities".*

Strokes are a major problem of public health. About 1 million strokes are counted each year in the EU. Stroke is the leading cause of physical disability, the second most frequent cause of dementia and the third cause of death. One third of the stroke cases display a fatal outcome and one third of survivor patients suffer from long-term disability.
The biology of stroke underlies multiple mechanisms (atherosclerosis, cardiac disease, small vessel disease etc...) influenced by risk factors (hypertension, smoking, diabetes, obesity, dyslipidemia etc...). The stroke occurrence and the infarct size can be influenced at different levels by genetic and environmental factors which influence hypertension, or interact with other risk factors such smoking, or contribute directly to atherosclerosis.
Today, basic and clinical research aims to consider the neural tissue distal to occluded vessels, the "ischemic penumbra". In this area, death mediators and multiple mechanisms (energy failure –i.e. ATP-, cortical spreading depolarization, inflammation, excitotoxicity, oxidative and nitrosative stress, calcium overload etc…) lead to infarcted tissue.
In term of treatments and clinical trials, multiple options are pursued:
(1) Thrombolysis with rtPA of occluded arteries in case of acute stroke,
(2) Combination of systemic thrombolysis with interventional methods of recanalization,
(3) Penumbra imaging (MR-based patient selection),
(4) New thrombolytic agents (desmoteplase [DIAS III], plasmin trials,...)
(5) Enhancement of cerebral blood flow (inflatable balloon into the aorta).
In the alteration of cerebral blood vessels, roles of risk factors are also considered in oxidative and nitrosative stress, 2 mediators of ischemic injury. As example, cardiovascular risk factors increase reactive oxygen production of multiple signaling pathways (superoxide-producing enzyme NADPH oxidase, xanthine oxidase, etc…) and lead uncoupling of nitric oxide synthase (NOS) and inactivation of nitric oxide, a vasodilator with anti-aggregant, anti-proliferative and anti cell-adhesion properties. This last point could be an important target in the stroke research.
Besides oxidative and nitrosative stress, others mechanisms contribute to cell death such excitotoxicity and calcium overload implicated in the early stages of infarct expansion, and the cortical spreading depolarization (CSD). The CSD process requires high levels of extracellular glutamate and potassium leading a high level of energy consumption, a drastic disruption of ionic gradients, and slowly propagating waves of massive depolarization of neurons and astrocytes. Using NMDA receptor antagonists could be an opportunity to limit infarct expansion.

Unfortunately, it's complicated to use clinical therapies based on these fundamental knowledge because of the various cellular types (astrocytes, neuron, microglia, endothelial cell…) participating in the pathophysiology of stroke. Thus, envisaging clinical therapies requires considering the neurovascular unit. One of strategy could be therapeutic hypothermia reducing brain metabolism (oxygen consumption, glutamate release, the production of radical oxygen species and peri-infarcts depolarizations) and inflammatory markers.

European projects (EUSTROKE and ARISE) have recently merged into the European Stroke Network which aims to develop major research themes such neurovascular unit, regeneration, neuroprotection and brain-immune interactions (role of immunodepression, effects of antibiotics, establish predictive and sensitive clinical markers…) and the biphasic role of inflammation (efficacy of key anti-inflammatory strategies, determination of the effects of systemic inflammation induced by infection or atherosclerosis on stroke outcome, tests of new inflammatory targets…). For this purpose, the network has established platforms for animal models, neuroimaging and clinical trials. So in this context, what are challenges and opportunities?
After a first stroke, about 20% of patients become demented. Because vascular cognitive impairment (VCI) is the second most common cause of dementia following Alzheimer's disease and has an important impact on stroke outcome (interfering with rehabilitation therapy), VCI is definitely a major challenge for treatments. Many cases cognitive impairment develops without clinically recognizable strokes. These vascular accidents are named silent brain infarcts and are associated with subtle deficits. The majority of them are caused by cerebral small vessel disease (CSVD). They are easily detectable by MRI and offer a target for preclinical diagnosis and prevention. They are mostly localized within central brain structures and diffuse white matter lesions reflecting various degrees of axonal loss, demyelization, gliosis etc…

Little is known about the vascular alterations but clinical data are available concerning CSVD. Indeed, vessel occlusions leads lacunar infarcts and diffuse white matter changes should be caused by chronic ischemia. Moreover, small arteries are reactive to local and systemic factors. For example, hypertension constitutes the most important risk factor inducing structural and functional changes in small arteries.

Actually many research areas are investigated:
(1) Identification of mendelian variants (ex: identification of HTRA1 mutations in consanguinous families with a cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). Expressed throughout the body, HTRA1 encodes a serine protease inhibiting cell signaling through TGF-b and related proteins. In case of vascular fibrosis, it has been shown an increased of TGF-b signalling.)
(2) Development of cellular and in vitro models and animal models (ex: mouse model for CADASIL with mutations in the Notch3 gene causing a variant of small vessel disease with axonal loss, demyelination, vacuolization, glial activation, functional hemodynamic deficits and an increase in vascular myogenic tone)
(3) Hemodynamic studies (ex: functional studies on blood flow)
(4) MRI and PET studies in patients with small vessel disease (ex: high field MRI at 7 Tesla allows to directly visualize perforating arteries with a diameter as small as 250 microns as well the significant reduction in the number of stems and branches of lenticulostriate arteries in hypertensive as compared to normotensive patients)
(5) Clinical trials (ex: SPS3 trial (secondary prevention of small subcortical strokes) which compares in the small vessel disease dual antiplatelet therapy (aspirin+clopidogrel) with aspirin monotherapy and the blood pressure.only one targeted trial emerge)
(6) Omics approaches (ex: detection of 9p21 risk locus for coronary heart disease, myocardial infarction, atherosclerotic stroke, artery disease (abdominal aortic aneurysms and intracranial aneurysms).
(7) In vivo microscopy,
(8) Neuropsychology,
(9) Industrial research and news targets, etc….

In conclusion, funding of collaborative programs by EU allowed to progress in major achievements but more challenges have to improve such research in cerebral small vessel disease (a major cause of ischemic stroke and vascular cognitive impairment), silent strokes and chronic ischemia. All these actions necessity coordinated research from different fields.

Annex I, Scientific Advisory Board

NEURON Scientific Advisory Board

Prof. Dr. Carlos Caltagirone, Italy
c.caltagirone@hsantalucia.it

Prof. Dr. Celso Arrango Lopez, Spain
carango@hggm.es

Prof. Rafael Maldonado, Spain
rafael.maldonado@upf.edu

Prof. Dr. Christophe Mulle, France
mulle@u-bordeaux2.fr

Prof. Dr. Ana-Maria Zagrean, Romania
azagrean@gmail.com

Annex II, List of Participants

NEURON Meeting Participants

Dr. Julio Barbas, Ministry of Science and Innovation (MICINN), Spain
julio.barbas@mec.es

Dr. Howard Bergman, Fonds de la recherche en santé du Québec, Canada
hbergman@frsq.gouv.qc.ca

Prof. Bernard Bioulac, Centre National de la Recherche Scientifique, France
bernard.bioulac@cnrs-dir.fr

Prof. Alexis Brice, INSERM, France
brice@upmc.fr

Dr. François Bourre, CNRS France
francois.bourre@u-bordeaux2.fr

Dr. Gaspar Giner-Abati, ISCIII, Spain
gginer-abati@isciii.es

Dr. Joanne Goldberg, FRSQ, Canada
jgoldberg@frsq.gouv.qc.ca

Dr. Jenifer Clark ANR France
Jenifer.Clark@agencerecherche.fr

Dr. Rafael De Andrés-Medina, Fund for Health Research (FIS), Instituto de Salud Carlos III
rdam@isciii.es

Priv. Doz. Dr. Marlies Dorlöchter, DLR Projektträger des BMBF, Germany
marlies.dorloechter@dlr.de

Dr. Rainer Girgenrath, DLR Projektträger des BMBF, Germany
rainer.girgenrath@dlr.de

Dr. Benny Leshem, Israeli Ministry of Health, Israel
benny.leshem@moh.health.gov.il

Dr. Nancy Mason MacLellan, CIHR Canada
Nancy.MacLellan@cihr-irsc.gc.ca

Dr. Herbert Mayer, FWF - der Wissenschaftsfonds, Austria
herbert.mayer@fwf.ac.at

Dr. Petra Pütz, DLR Projektträger des BMBF, Germany
petra.puetz@dlr.de

Dr. Mika Tirronen, Academy of Finland, Finland
mika.tirronen@aka.fi

Prof. Dr. Ana-Maria Zagrean, Romania
azagrean@gmail.com