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EDITORIAL
Consensus Statement on European Brain Research: the need to expand brain research* in Europe – 2015

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Recommendation

The brain – the most complex organ of mankind and the challenge to understand its function and to cure its disorders

The brain is the most complex organ of the human being. It provides and controls virtually every function of the body including rational thinking, emotions, heart beat, breathing, food and fluid intake, sex, etc. Disorders of the brain are more complicated to analyse, diagnose and treat than other diseases. These brain disorders (to name just the most common ones - depression, Alzheimer's dementia, schizophrenia, stroke, migraine, sleep disorders, Parkinson's disease, pain syndromes in particular back pain, addiction to alcohol and other substances) give rise to a far higher level of disability, including admissions to hospitals and nursing homes, than is widely recognised. Health economists have calculated that brain disorders may cost as much as 45% of the annual health budget of Europe, totaling around Euro 800 billion (Gustavsson *et al.*, 2011; DiLuca & Olesen, 2014). With an aging population in Europe the prevalence of the most common neurological and psychiatric disorders will dramatically increase and we have not found cures or means to delay or reduce their burden and economic impact, as well as the burden of care-givers and the loss of productivity and employment associated with this.

Knowledge of brain function has substantially increased over the last decades

At the same time, from a position of relatively limited knowledge about the brain some 50 years ago, our basic understanding of the nervous system has expanded markedly since then. Indeed, European basic and clinical neuroscientists have played a major part in this success story. The availability of astonishing new technologies, particularly over the last ten years, has greatly aided this development. It is an area of research in which many young people in both the life and the physical sciences wish to work –the brain represents one of the last truly great frontiers. Thanks to dedicated support and commitment from funders and scientists in recent years, Europe is now at the forefront of the international effort both to understand the brain through basic science and to apply this knowledge in practical and clinically relevant ways.

Targeted European funding of brain sciences has put Europe at the international forefront – to find the cure of brain disorders must get top priority

In line with the above, the European Commission provided comprehensive support for brain research in the 7th Framework Programme. Brain Research was finally and rightly considered a priority to be endowed with the necessary, targeted financial resources: more than EUR 3,1 billion has been dedicated to brain-related research since 2007, funding 1931 projects. Thanks to these efforts we better understand the diseases and cures are getting closer, but we are not there yet. Thus, at this stage of development in the research towards real solutions, continued support for brain research is still a real and pressing need.

From basic neuroscience via clinical trials to product approval – the enforcement of the translation workforce in European brain research

Discoveries and advances in basic neuroscience are the prerequisites for describing the normal function of the nervous system and revealing the etiology and pathophysiology of brain diseases. To move such discoveries forward for the benefit of patients however, we need translational and clinical experts, ideally trained in the laboratory as well as in the clinical setting. These experts will provide the

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*In this document brain research is used to refer to both fundamental curiosity-driven and translational research on disorders of the brain, spinal cord and peripheral nervous systems and to cover both psychiatric (mental) and neurological disorders.

†The author passed away on the 2nd October 2015.

The board of the European Brain Council (EBC) adopted the present document on November 26th 2015.

crucial bridge to cross the divide between bench and bedside. An additional vital element of European brain science will be the highly trained clinical study physicians who can generate high quality and reproducible data in large clinical trials. Researchers at all levels are required for the European population to benefit from discoveries and advances in basic neuroscience to be translated in new diagnostics tools and treatments for brain disorders.

In summary, it is critical that neuroscience must receive the highest priority in political attention and the largest part of the European budget for medical research with the goals to reduce the burden of brain diseases to patients, spouses/carers and society at large, by slowing down or even preventing diseases of the brain.

Accordingly:

- We call upon the European Commission to recognise the continued major needs in basic and clinical brain research, and the current lack of targeted research support.
- An immediate step could be for the Commission to liaise with the European Brain Council to optimise ways of supporting services for patients and research.
- Directorate General for Research and Innovation must explore ways to better sustain brain research within Horizon 2020, the Marie-Slodowska-Curie programme, and through other platforms.

By establishing such policies the European Commission would invigorate the return of pharmaceutical and other health-industry research to Europe, thus reversing the trends of the last few years with enterprises and researchers migrating to other continents or disappearing from brain research altogether.

EBC – the one voice representing all stakeholders in brain sciences in Europe

European brain science is promoted through the activities of a number of societies that together form the European Brain Council (EBC). The EBC was established in 2002 and encompasses all major scientific and clinical societies, industry and patient organizations – related to brain science and brain disorders. One of its principal aims is the elimination of the major discrepancy between the huge impact of brain diseases and the practical implications of understanding normal brain function, on the one hand, and, on the other hand, the modest financial resources allocated to brain research, for training the skilled work force, for teaching and for care of patients with brain diseases.

The Federation of European Neuroscience Societies (FENS) represents the largest scientific association in Europe, with for more than 24 000 members belonging to 42 scientific societies. The mission of FENS is to advance research and education in the field of neuroscience. It has succeeded in its primary endeavour of creating a platform for exchange and for catalysing a critical mass of European neuroscientists, in various ways including its biannual meeting with over 6000 participants. FENS has led the development of this report.

The other members of EBC that have contributed to this report are the European Academy of Neurology (EAN) that was founded in 2014 following a merger of two European neurological societies (ENS and EFNS). The EAN represents one of the largest medical scientific associations in Europe, with for more than 25 000 members belonging to 46 national neurological societies. The European Psychiatry Association (EPA) that represents European psychiatrists and the European College of Neuropsychopharmacology (ECNP) that represents translationally-oriented psychiatrists and other clinical neuroscientists. All these professional societies host annual meetings with many thousands of delegates from all over Europe and many other countries. EBC also represents GAMIAN Europe (Global Alliance of Mental Illness Advocacy Networks-Europe) and EFNA (European Federation of Neurological Associations), the umbrella for all patient advocacy groups in Europe related to psychiatric and neurological diseases. Alone these two patient organisations represent the needs of more than 100 million citizens living with brain disorders, not to speak of the millions of affected families, carers and thus representing a large block of the electorate.

This partnership of expertise is vital to secure the future of brain research in Europe, particularly as the EBC's study of the cost of brain disorders has revealed a cost to the European economy and national health budgets of nearly €800 billion per annum and that brain disorders currently affect 179 million Europeans. The costs of brain diseases for European society will increase considerably in the future due to the ageing of the population. Addressing these costs through intensified research and creating solutions is essential. Strengthened research, both basic and clinical, as well as the development of a strong European platform for brain research is needed to face what is becoming a societal emergency.

The place of basic science in Europe

At a time when countries across Europe are facing major economic difficulties of various kinds, it is understandable that the European Commission, MEPs and other decision-making entities should seek concrete information about the impact that science is having on the well-being of European citizens. Given this, there is a clarion call for greater 'translational' potential of basic science. To the working scientist at the lab bench, nothing could be more rewarding than to discover that some aspect of their research has found application in new enterprise, in education or in health care. However, the path to achieving this is far from straightforward.

Experienced and talented scientists – and Europe has many – are now aware of the likely market impact of a product or of how their work may integrate with that of others to be of commercial value. What such scientists tell us time and again, and history tells us likewise, is that basic research yields amazing and sometimes unexpected gains.

We present here the views of neuroscientists from all parts of Europe – north, south, east and west.

Consultation with young and senior scientists

FENS, together with the Kavli Foundation, recently made an open-call to create a network of 20 of the most outstanding young neuroscientists across Europe. They meet periodically to share ideas and discuss 'hot topics' in contemporary neuroscience. Their reflections on both the current area of brain science and what they judge to be the next 'grand challenges', offer a snapshot of what young neuroscientists in Europe actually think (Table 1).

Their comments reflect a mature awareness of the importance and costs of brain disorders. At the same time, the group wisely noted that progress generally emerges from better understanding rather than mere noble aspiration, and they made numerous comments about the reliance of clinical service and clinical research upon fundamental basic science. They raised the need for greater interdisciplinarity – a term referring to the sharing of ideas across research disciplines, including the transmission of ideas from chemistry, physics and engineering to clinical research. Arising from such an approach is the exciting possibility of better understanding of the neural circuits of the brain that mediate its diverse functions and how they go wrong disease and how they contribute to the symptoms and outcomes of diseases. Our understanding of brain disor-

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ders will surely rely upon new molecular tools, of the kind that have emerged from the important work of the European Molecular Biology Organization (EMBO), and with these will come new approaches to the treatment of major neurological and psychiatric brain disorders such as depression, Alzheimer's disease, schizophrenia or stroke. From the contributions from the FENS-Kavli network, there was a real sense that, despite Europe being a very attractive place for our young scientists to work, they often have to rely on the tools, services and data-sharing repositories developed and adapted for the use of scientists in the United States rather than by their own facilities and researchers. Although there are some impressive major groupings of basic scientists, and some new initiatives (such as the Francis Crick Centre in London), Europe does not yet have in the life sciences facilities akin to CERN for the physical sciences. The perceptive comments of members of the new FENS-Kavli network often recognise the challenge, but speak positively of the opportunities before them:

> "In work on dementia, we have failed to translate solid science into effective therapeutics with an abysmal 99.6% failure rate in clinical trials. But, using a combination of cognitive profiling, genetics, and *in vivo* and post-mortem imaging of cohorts of patients, we are building an in-depth understanding of what goes wrong in the brain."

> "It is crucial for Europe to keep science high up in the political agenda."

> "We have a realistic chance to increase the life-quality of sufferers from brain disorders as well as lowering the cost to society. Europe has had a leading edge in research into many neurological disorders, especially due to excellent cross-country collaboration between European nations, combining research data and experience. In the last five years, applications of young researchers have increased by more than 70%, demonstrating the wish of young scientists to work in Europe is strong. But we need to maintain European competitiveness in research related to diseases of the nervous system and to hold on to the best-trained young European scientists in this discipline."

FENS also conducted a consultation with more senior European neuroscience leaders (Table 1). Their perspective differs in generally reflecting longstanding experience of how research evolves and how long it takes for major challenges to be met:

> "It is the nature of basic research that we do not know what the applications will be. Yet I believe that a better understanding of neural circuits, and their relationship to behaviour, will benefit the entire span of psychiatric and neurological diseases and syndromes, in the long run, simply because we will understand the neural codes better."

> "Neural disorders are becoming the largest burden in biomedicine. We need to have more quantitative knowledge of anatomy, plasticity and gene expression in different circuits, not only in laboratory animals but also humans. We also need to functionally understand the circuits involved in memory and action, as this knowledge will allow us to tackle the most devastating disorders, and also to design better education systems and policies in our society."

> "There is still a tremendous amount of uncertainty as to the nature, causes, and treatment of most brain disorders. To address these challenges, there is wide agreement that the more promising discoveries are now those that take place at the macroscopic level. Paired to new techniques that can target circuits and systems, discoveries at this level promise to provide a new avenue for innovation in the understanding and treatment of brain diseases."

> "A good example of how basic research in the past fuels benefits now and in the future is the work in the 1960's on catecholamine uptake systems into neural tissues which developed into an understanding of amine transporters and the development of the various families of antidepressant therapy".

Challenges

From the full range of comments received, a variety of major challenges have been identified for which there is collective agreement about their urgency and tractability. These are presented under distinct headings: (i) making the brain, (ii) understanding the causal mechanisms of how it works and goes wrong, (iii) information processing, (iv) emerging new technologies, (v) neurological and psychiatric brain disorders of children and adults (vi) Computational neuroscience and the place of physical scientists alongside life scientists in bringing their skills and concepts to bear on hitherto difficult problems.

Making the brain: developmental neuroscience

The development of body and brain is one of the most amazing and fascinating events in the world of biology. From a fertilized ovum, there emerges a fully formed body with all its diverse organs and ability to survive – all happening within the space of nine months. At birth, a baby's brain may be immature, but it already has approximately 100 billion brain cells to help it understand the booming and buzzing confusion of life outside the womb.

Developmental neuroscience is now a mature field within the brain sciences – numerous critical genes and processes have been identified. The challenge is now to apply our new knowledge of developmental programmes such as migration or axon guidance, to systems neuroscience and, importantly, to developmental diseases. Establishing bridges between developmental neuroscience and systems neuroscience is essential. What are the consequences of alterations in developmental processes for the functional adult central nervous system, and even more importantly, for defining altered risk or susceptibility to devastating brain disorders later in life?

Molecular and biochemical studies focusing on brain development also need to be complemented by functional studies that will help to make sense of the properties of neural networks and circuits. With respect to human development, there is a strong tradition in developmental psychology but a dearth of studies of the developing human brain. The baby's brain can easily still be considered a virtual terra incognita. Babies have extraordinary behavioural and learning abilities, but we know very little about which brain networks underlie these abilities. Understanding the development of the human brain *in utero* and in the first years of life is crucial to understanding the very frequent developmental pathologies of dyslexia, dyscalculia, attention disorders and autism. Schizophrenia and similar complex disorders must also be considered as developmental conditions whose impact only becomes visible late in adolescence. Prospective studies of schizophrenia, for example, are rare but the opportunity to capitalise on contemporary developmental neuroscience is considerable.

Possible Horizon 2020 Projects

- The bridge from brain development to mature circuit function and dysfunction.

Understanding causal mechanisms: linking cellular/molecular mechanisms to complex behaviours and disease states

Another major challenge in neuroscience is a variety of 'bridging' problems. Understanding the mechanisms that bridge multiple spatial and temporal scales, i.e. the task of linking the activity of individual components (e.g., molecular biology, genetics, and neuron networks) to the overall complex dynamic behaviour of the brain, remains one of the greatest challenges in neuroscience. It is, however, vital for progress in understanding normal and abnormal brain function.

We need a clear understanding of how molecular processes act at the level of specific neurons to affect information processing at the level of circuits, and finally how these circuit level processes are integrated within neural systems to control the behaviour and cognition of the whole animal in both normal and pathological situations (which are often caused by alterations at the genetic/molecular level). To appreciate the complexity of the system, we need bridges between different research fields in order to understand how the brain integrates its activity with that of other systems including the immune system, metabolism and vascularization, and how - in a given brain disorder - this integrative brain function is harmed or even lost.

To understand how neural circuits operate, we need access to activity of large numbers of neurons at the same time, and to identify the morphology and genetic expression patterns of the neurons from which recordings are being taken. Much of the population code may lie at the level of synapses, not entire neurons, and the codes may be distributed. If so, we will need access to those distributions, for example single-spine imaging in combination with whole-cell recordings, ideally in awake behaving animals. This type of analysis is technically challenging and likely beyond the capacity of all but a very few laboratories.

Access to increasing amounts of data will necessitate and drive the creation of better analytical methods, but the biggest challenge will then be the development of theories and concepts that allow us to look for meaningful patterns within such 'big data'. Behaviour, in particular, needs to be broken down into the appropriate elements that correspond to addressable physiological processes in the brain. Realizing both of these – serious quantities of data and the theoretical framework to deal with it - will lift neuroscience from a science replete with correlations to one that is based on mature theories and models. Much of the theoretical development that will take place will be quantitative, theoretical neuroscience that should gradually become more integrated with mainstream experimental neuroscience.

Only by understanding how these levels interact will we be able to develop a clear understanding of how neuronal processes control behaviour and physiology and thereby define the strategies to tackle important societal challenges of brain disorders. In fact, a better understanding of neural circuits, and their relationship to behaviour, in the long run will benefit the entire span of psychiatric and neurological disorders, simply because we understand the neural codes better. A good example is perhaps Alzheimer's disease, which will benefit from the growing understanding of neural circuit mechanisms and connectivity in the entorhinal cortex and hippocampus, as well as the nature of cell types in these areas, whose vulnerability may provide clues to the factors that trigger the development of the first signs of Alzheimer's. Tracing and connectome studies may become of increasing importance with the recent proposals of a prion-like component of several neurodegenerative disorders including Parkinson's disease.

Possible Horizon 2020 projects

- 'Big data' projects, which may emerge in many different ways, notably in the mental health domain, and in specific projects on neurological disorders such as channelopathies, and in basic science projects driven bottom-up from molecular roots or top-down from analyses of behavior.

Information processing: what the brain does

The brain controls behaviour through an interlinked set of elaborate mechanisms: sensing the world around us (e.g. seeing) and the world within (e.g. proprioception); the transformation of this sensory input into an object-oriented understanding (via perception); linking this knowledge with stored information from memory; and the organisation of actions and habits guided by emotion and motivation. We understand a lot about theses mechanisms, but many aspects of these processes remain a mystery, especially fundamental concepts like numerosity and decision-making, and also how they are impaired in neurological and mental health disorders. Major targets of basic research include:

Perception: How does the brain achieve robust, invariant, multimodal perception? Humans rapidly recognize faces, objects, and written words. These aspects of perception are highly robust to major changes in size, location, illumination, point-of-view (invariance) etc. No current computational algorithm is able to match this feat.

Magnitudes: How does the brain represent and compute with magnitudes things such as spatial coordinates, time, or number? Humans and many animals are endowed with the capacity to represent and compute with various magnitudes: they can use spatial maps to navigate from point A to point B, determine the time remaining before a certain event, or add or subtract two numbers. Understanding these abilities is crucial to characterize how the human brain performs computations.

Concepts: How does the brain extract and represent concepts? Humans do not stop at identifying pictures, but also extract the conceptual structure of their environment. We generate conceptual categories (e.g. animals versus tools) and conceptual similarities (for instance, a dog is more similar to an elephant than to a car). Why do all humans, in all cultures, parse the world into approximately similar categories? Understanding the origins of concepts is essential for diseases such as Alzheimer's and other forms of dementia, which are characterized in part by a degradation of the semantic network.

Probabilities: How does the brain compute with probabilities? A large body of behavioural and neuroscience research has demonstrated that the brain uses statistical computations to learn the structure of the world, to predict the likelihood of future events, and to take decisions based on the most likely outcomes of actions. By contrast, current computers primarily use a deterministic approach. Learning how the brain computes with probabilities is already having an impact on the newest generation of computing devices, but there is a lot more to learn from real neural networks.

Decision-making: How does the brain make decisions and monitor them? Although we now understand that the brain makes decisions through the accumulation of probabilistic evidence, we do not understand how it quickly identifies the relevant evidence, how it selectively accumulates it over space and time, and how it routes it to the relevant output systems. Furthermore, humans exhibit a sophisticated ability for second-order thinking about their decisions, generating a sense of confidence, regret, knowledge of their limits – all features, which would be extremely useful to mimic in artificial devices.

In addition to these important processes, which can have a major effect on economic decisions for example, there are additional unknown aspects that are both captivating and also directly relevant to the major challenges of mental health disorders:

Consciousness: What is conscious processing? Far from being an unreachable goal, the issue of how consciousness arises from brain networks is becoming increasingly accessible to current research methods. In the domain of perception, we can identify minimal contrasts between conscious and non-conscious processing of the same stimulus and then study how they differ using brain-imaging techniques. In the clinic, consciousness can be studied through examination of anaesthesia, coma, or vegetative state. Although considerable progress is being made and the knowledge is already being used in clinics both to diagnose disorders of consciousness and to speed up the recovery of coma or vegetative patients, much more work is needed to put us in the position in which truly understand consciousness.

Self-consciousness: How does the brain generate a sense of self? All animals possess a mental representation of the body that maps the location of the limbs in space and the limits of their body with respect to the environment. Humans also know which actions are their own, and which arise from the environment or the act of others. A sense of self is also present in autobiographical memory. These systems can be severely degraded in pathologies such as Alzheimer's disease or schizophrenia, and fundamental understanding of how they operate and can be remediated.

Human singularity: What aspects of brain function are uniquely developed in humans? Language is a candidate – and it is essential that we better understand how language networks operate and develop if we are to understand pathologies such as aphasia and dyslexia. A second candidate is theory of mind – the capacity to represent the thoughts of others. This ability seems severely and specifically degraded in many cases of autism. By definition, there will be no detailed animal models of these high-level pathologies as they are specific to humans, so a strong research focus on methods capable of exploring the human brain (e.g. higher-resolution brain imaging techniques) is crucial.

Possible Horizon 2020 projects

- Cognitive neuroscience - connections between fundamental animal work and studies of the human brain in health and disease, and the development of new techniques to rectify such disorders.

Emerging new technologies

It is a truism in science that new technologies open new windows to discovery. Despite the imagination and pioneering work of many of our scientists, Europe is at serious risk of falling behind in the development of new technologies. Examples of issues that need to be considered:

The human brain: New ways to study and monitor the activity of the human brain including high-resolution recording/imaging techniques and safe optogenetic techniques that combine optical activation with viral genetic tools.

Big data analysis: In common with many other sciences, we need new methods for big data analysis and the integration of multi-source, complex data to formulate new theories.

Measurements of synaptic plasticity and degeneration: Through plasticity at synapses, circuit function can change, eventually leading to pathological behaviour. With the advent of optogenetics, a seamless integration of these observations is now within reach. While there is no doubt that optogenetics has been a game changer (a technique first developed in Europe), the method is so powerful that some manipulations may elicit behavioural changes that have nothing to do with the normal or pathological function of the brain. Therefore, functional imaging with cellular resolution in freely moving animals using genetically encoded calcium indicators in combination with electrophysiological approaches may become the observational method to tailor meaningful optogenetic interventions. The hope then is that by identifying the pathological neural activity that really drives symptoms, one can design blueprints for novel pharmacological interventions, and allow this to be an impetus to overcome the current deadlock faced by pharmaceutical companies.

Possible Horizon 2020 projects

- Supplement large educational programmes with 'hotel' support for expensive new technologies, that individual laboratories may not be able to afford, in order to provide state-of-the-art training of emerging scientists as well as create major neuroscience technology hubs to more rapidly advance new techniques in pre-clinical and clinical research.

Brain and mental health disorders - Neurological and psychiatric brain disorders of children and adults

Both neurological and psychiatric disorders are the largest burden and challenge in our society. Discoveries at the microscopic level (receptors, synapses, neurons) have already found application in the prevention and treatment of brain disorders: pharmaceutical and biotech companies have developed small molecules that are highly effective in targeting these sites. However, this approach has peaked in its effectiveness and the pace of improvement is now greatly diminished. It is widely recognised that a reason for this is the need to incorporate understanding of disorders at the circuit level. One example of this is the window of increased synaptic plasticity in the weeks after stroke in humans. Changes in synaptic plasticity occur in animal models, which allow much greater transformation of circuits than is usual in the adult brain, but whether this occurs in humans is unknown. If we can determine whether this is indeed the case, it could have enormous impact on treatment strategies and development of drugs to extend or deepen this basic mechanism.

Europe has been at the leading edge in research into many neuropsychiatric and neurological disorders, especially due to excellent existing and developing cross-country collaboration between European nations, combining research data and experience. Examples are recently initiated or existing networks in Mood disorders (bipolar disorder and depression), Alzheimer's disease, stroke, schizophrenia, Parkinson's disease, restless legs syndrome, insomnia, multiple sclerosis, epilepsy or neuropathic pain to name only well known entities. All these collaborative efforts are now ready to be maximally exploited to the benefit of patients provided sufficient funding is available. Research related to these diseases that have a serious impact on the mental and physical health of individuals, as well as their employment and productivity, has entered an unparalleled era. The introduction of novel technologies means we are placed for the first time to capitalise on them to develop and introduce new treatments and hence reduce the disability caused by them. Therefore, we have a realistic chance to increase the life quality of sufferers as well as lowering the cost to society.

Possible Horizon 2020 projects

- A major impetus in the domain of brain health – a major cost on the health systems across Europe – for example as recommended by the ROAMER project, is the development of European centres for mental-health research or as recommended by EAN, to create a network of neuroscientific and neurological clinical research centres of excellence throughout Europe.

Computational Neuroscience and data repositories

The large number of technological advances in basic neuroscience has led to an exponential growth of data production relating to various aspects of the brain, under numerous different conditions and across several species. Computational neuroscience approaches including modeling and large scale data analysis/integration methods, will be essential to turn these data into a better understanding of the brain and help develop new tools for dealing with brain disorders.

The biggest challenge in computational neuroscience is to develop biologically-based mathematical and statistical methods to meet this critical need. Key problems include understanding the mechanisms that bridge multiple spatial and temporal scales, linking the activity of individual components (e.g., molecular biology, genetics, and neuron networks) and their interactions to the overall complex dynamic behaviour of the brain and nervous system. One example is the need for ways to compare and unify the large number of models that have been validated against different data derived from different species and are proposed to describe the same regions of the brain. In order for computational neuroscience to address these challenges, there is a need for:

- Open data repositories developed by scientists that can be used for model development.
- Open code repositories for developed models and the data used to constrain them.
- Better opportunities for publishing theoretical/computational findings in journals traditionally accepting experimental papers so as to promote visibility, inspire and guide new experiments that will test hypotheses.
- Closer collaborations with experimentalists to establish a feedback loop between theory-driven experimentation and discovery-driven model refinement.
- Computational neuroscience has moved from the fringe of neuroscience to its very heart. In the coming years the anticipated explosion of highly complex data sets in neuroscience creates the urgent need for properly trained data analysts and modellers to develop and utilise high dimensional analytical tools. Furthermore, a closer interaction between basic and clinical neuroscientists and computational neuroscientists is also needed in order to generate realistic and useful data sets.
- This necessitates a refocusing of funding allocation and quality assessment, and also presents a great opportunity to interconnect European neuroscience and to integrate - and profit from - the maths and physics focused science infrastructure in younger member states of the European Union.

Understanding and Improving Drug Delivery to the Brain

Increasing insight into the pathophysiology of brain diseases, be they metabolic, inflammatory, traumatic, immunological, neurodegenerative or oncological, has lead to the development of many promising potential therapeutic agents that may have a tremendous impact on disease processes. The brain, however, is well protected against influx of many reagents by the blood-brain barrier which does not allow the passage of large molecules, including antibodies. This is particularly important as monoclonal antibodies that can be tailored to target many relevant dysfunctional molecules in a large variety of disease classes.

The biggest challenge in the design of new neuro-therapeutics, is to enable them to attain an even distribution within the brain beyond the blood brain barrier.

- A concerted effort is needed for an integrated approach where technologies for interstitial delivery, either directly or by specific manipulation of the blood brain barrier, are developed and combined with molecular imaging technologies to monitor the delivery.
- Pharmaceutical industry, especially pharmaceutical and medicinal chemistry, must be encouraged to embrace the vast

opportunities in embarking on drug developments in which neurodegenerative processes are stalled or reversed by disrupting accumulation of neurodegenerative products, many of which are already known.

- In doing so, industry has to work closely with basic scientists for the extrapolation of models to the human situation, and the framework of clinical trials has to be reworked to allow for early evaluation of new delivery models without exposing the manufacturers to unaffordable and unrealistic insurance risks. This includes provision of a regulatory framework in which the stakes of a drug manufacturer, a separately patented delivery formulation and a proprietary delivery methodology, are mutually protected.
- Brain banks for as many brain diseases as possible, have to be established as has already been pioneered for some prototypic disorders. These need to work within the framework of European networks so that drug targets derived from basic science disease models can be correlated to the real human *in vivo* situation.

Conclusions

For urgent humanitarian, medical, scientific, political and economic reasons, it is imperative that there is a step-change in the prevention, treatment and management of the brain disorders that will affect one-in-four Europeans in their lifetime.

Major developments in a range of non-communicable disease areas has clearly demonstrated that where there is dynamic collaboration between all parties committed to making progress – encompassing patient organisations, academics, scientists, medical experts and industry – then exponential progress can be achieved.

This document sets out very clearly what needs to happen to escalate progress and EFNA and GAMIAN welcome the document and its recommendations with great enthusiasm and commitment.

References

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