

## CONSENSUS DOCUMENT ON EUROPEAN BRAIN RESEARCH

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## Abstract

Psychiatric and neurological diseases combined represent a considerable social and economic burden in Europe. A recent study conducted by the European Brain Council (EBC) quantified the 'cost and burden' of major brain diseases in Europe, amounting to €386bn per year. Considering that these costs will increase exponentially in the years to come due to ageing of the European population, it is necessary to act now in order to curb this increase and possibly reverse the trend. Thus, establishing a strong European platform supporting basic and clinical research in neuroscience is needed to confront the economic and social challenge posed by management of brain diseases in European countries. To setup a platform for discussion, EBC published in 2006 a *Consensus Document on European Brain Research*, describing needs and achievements of research in Europe and presenting proposals for future research programs. Since 2006, European research in neuroscience has advanced tremendously. The present document represents an update elaborated to reflect changes in research priorities and advances in brain research that have taken place since 2006. The same approach and format have been used here as in the previous version. Multinational and multidisciplinary teams have once again come together to express their views, not only on the current strengths in European research, but also on what needs to be done in priority, hoping that this update will inspire policy makers and stakeholders in directing funding for research in Europe.

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## Chapter I: Brain development, plasticity and ageing in health and disease

### Section Editor: Monica Di Luca

#### Theme I. 1: From developmental disorders, fetal, perinatal and postnatal insults, to genetics and basic mechanisms of brain development

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##### Background

Brain development is regulated by complex neurobiological programmes, small deviations can give rise to severe brain diseases such as autism, schizophrenia and lissencephalies, or predispositions to brain whose onset occurs later in life. Most psychiatric diseases produce their first symptoms in childhood or early adolescence (Paus *et al.*, 2008), but even psychiatric disorders that manifest in adulthood, such as schizophrenia or bipolar disorder, are associated with abnormal brain development. Abnormal brain development therefore contributes to a wide range of psychiatric and neurological diseases. Since the burden of these diseases is extremely high in Europe, and since many of them are untreatable, understanding the biological processes that underpin brain development is of critical importance.

##### Past achievements in Europe

In the last 5–10 years European researchers have capitalised on advances in genetics to identify regions of the human genome that contain information relevant to specific brain diseases. The localisation of these regions has been very successful (Merikangas *et al.*, 2009; Sebat *et al.*, 2009), but understanding how genetic variation within them gives rise to brain diseases less so. Most current research programmes have adopted a top-down approach, taking a particular disease as their starting-point. Yet in schizophrenia, for example, genetic and phenotypic heterogeneity are known to reflect the complexity of neurodevelopmental processes (Sebat *et al.*, 2009). Only a few EU programmes have addressed more fundamental questions regarding brain development to date. These include Neurostemcell, Neugene, Dopaminet and mdDANEurodev. Recently, some countries have set up national networks for research into neurodevelopmental disorders. These national networks should, we believe, be expanded into European networks.

##### Proposal

We propose a more fundamental, neurobiological approach to studying brain development and how it may give rise to disease. The following issues need to be addressed:

1. If and how prenatal exposure to specific external factors such as maternal medication and physical insult affect prenatal brain development, increasing the risk of brain disease later in life.
2. How genetic programmes are generated and how they function to build specific neuronal groups in the brain.

3. What are the underlying neurodevelopmental defects in brain diseases.
4. Data from large-scale genomic studies and transcriptome profiling need to be translated into specific neurodevelopmental events, so that the effect of genetic deviations on those events can be explored. In particular, a comprehensive, interdisciplinary analysis of the function of candidate susceptibility genes in brain development is needed.
5. The molecular mechanisms that explain the progressive brain changes seen in early-onset brain disorders such as autism and childhood schizophrenia need to be assessed.
6. The effects of psychotropic drugs on the developing brain need to be assessed.

Furthermore, research should be based on endophenotypes, rather than on clinical phenotypes defined by diagnostic criteria, as is currently the case, in order to eliminate some of the heterogeneity that exists in those diagnostic groups, and make it easier to associate endophenotypes with genes of interest.

##### Significance of increased research

If we know the developmental defects that give rise to brain disease, it may be possible to correct or mitigate them in the pre- or perinatal stages of life, so reducing the overall burden of brain disease in Europe. Where the cause of those defects is discovered to be exposure to specific external factors, the defect might be preventable altogether. There is evidence, for example, that treatment of expectant mothers with antidepressants can cause behavioural abnormalities in their children (Noorlander *et al.*, 2008).

The initiatives we propose, combined with current initiatives, will provide the understanding that is needed to generate novel treatment strategies for patients with brain diseases – treatments that intervene with the underlying disease rather than just with its symptoms. Moreover, through collaboration with industry, Europe's role in the discovery of potential drug targets will become more important, at a time when the ageing of the population means the burden of brain disease is only set to grow.

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## Theme I. 2: From ADHD, autism and their animal models to signalling mechanisms and genetics

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### Background

Attention-deficit/hyperactivity disorder (ADHD), autism and autism spectrum disorders (ASD) are lifelong disorders, which represent serious challenges for society, both human and financial. Although they are the two common disorders whose genetic basis has been most clearly determined, no biological markers have been found for them. ASD occurs in about 0.5% of the population. Across different cultures and countries, the prevalence of ADHD is conservatively estimated to be 5% in school-age children, 3% in adolescents and 2% in adults (Sagvolden *et al.*, 2005). The defining characteristics of ASD are stereotyped interests, and social and language impairments. ADHD is associated with severe problems in arithmetic, computation and reading problems later in life, which lead to a lower work status and income than the individual's intelligence and abilities would normally predict. ADHD is associated with an increased risk for conduct disorder and depression, which in turn are associated with elevated risk for criminality and suicide, as well as attempted suicide, sexually transmitted disease and teenage pregnancy.

### Past achievements in Europe

The first forum for ADHD research (EUNETHYDIS) was established in Europe 15 years ago. The first international interdisciplinary ADHD research group gathered at any Centre for Advanced Study (CAS) was organised in Norway during the academic year 2004–2005, to bridge the gap between basic and clinical ADHD research. European researchers have contributed significantly to the recognition of both ADHD and ASD as neurodevelopmental disorders with strong genetic components (Sagvolden *et al.*, 2005; Jamain *et al.*, 2003). European researchers published the first comprehensive theory of ADHD, in which they explained how predisposing genetic and neurobiological changes interact with pharmacological treatments, and environmental and societal factors in the development of ADHD symptoms (Sagvolden *et al.*, 2005). European researchers have led the validation of animal models of ADHD (Pinto *et al.*, 2010). Other European researchers have proposed an animal model of autism, though it has yet to be formally validated (Anney *et al.*, 2010). Research on complex psychiatric disorders involves experts working in more areas of research than are found in any one European country.

### Proposal

ASD and ADHD are thought to arise from complex gene-environment interactions, where the latter may include exposure to neurotoxic substances (Sagvolden *et al.*, 2005). The reductions in dopaminergic functioning that are seen in ADHD can result from both genetic and non-genetic factors. Prenatal exposure to some polychlorinated biphenyl congeners seems to produce ADHD-like behaviour. Epidemiological studies have linked insecticide, herbicide and fungicide exposure to death of dopaminergic neurons by mitochondrial chain complex I inhibition. Tobacco smoke is perhaps the most ubiquitous environmental pollutant to which children are exposed. Studies are

therefore needed to investigate whether these chemicals can enhance ADHD and at which doses. Environmental factors have also been discussed in association with ASD, and research is needed to elucidate their role in the disorder.

In addition to those studies, the ongoing search for genes involved in these disorders must be intensified (Pinto *et al.*, 2010; Anney *et al.*, 2010). Several candidate genes for ADHD and ASD are involved in synaptogenesis and neuronal alignment and adhesion (Napoli *et al.*, 2008). It has been suggested that altered synaptic reinforcement and extinction processes define an endophenotype in ADHD that can be related dimensionally to inattention, hyperactivity, and impulsivity (Sagvolden *et al.*, 2005). Such insights may be useful, not only for the development of more efficient medication, but also in developing reliable and culturally appropriate behavioural screening tools. Advances in neuroscience will produce more precise knowledge about the neurobiological changes that take place in ADHD and ASD. We need to know how genes and chemicals alter subcellular as well as cellular and behavioural functions in order to understand these disorders. For both ethical and economical reasons, these studies will in many cases have to be performed on animal models.

### Significance of increased research

ASD and ADHD research not only provides an opportunity to understand brain function in the light of recent genetic, neurobiological and behavioural advances, it offers an equally important opportunity to turn such understanding to the benefit of the individual, family and society. The burden of caring for those affected will be lightened. Moreover, with the appropriate specialised care, affected individuals' chances of becoming productive members of society will only increase. Collaborations between European industry and universities have an excellent chance of translating their work on molecular targets in the brain into new medicines and improvements in environmental health.

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### Theme I. 3: From speech disturbances to basic mechanisms of language

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#### Background

It is estimated that approximately 7% of children suffer from speech and language disorders of developmental origin, with nearly half of those maintaining residual deficits into adolescence, despite intervention. In adults, persistent speech and language disturbances are common comorbid features of acute conditions such as stroke and head injury, and of degenerative diseases such as Alzheimer's disease and Fronto-Temporal Dementia. Across the age spectrum, the burden of speech and language problems for the individual and society is enormous. By interfering with communication, such problems undermine self-esteem, and prevent integration within the social milieu, and adjustment and/or return to school or work. In children, speech and

language disorders are a leading cause of learning disability, seriously interfering with literacy development and educational progress.

#### Past achievements in Europe

European research has had a profound influence in unravelling the neural basis of speech and language. The recent discovery of *FOXP2*, the first gene associated with speech and language, has ushered in the era of 'cognitive genetics', and provided a molecular entry point for studies into this uniquely human ability (Vargha-Khadem *et al.*, 2005). Large-scale studies have identified different subtypes of speech and language disorders and their co-morbid features, and have identified the role of polymorphisms in *CNTNAP2*, a gene regulated by *FOXP2*, in specific language impairment (Vernes *et al.*, 2008). The advances in multimodal neuroimaging are providing a comprehensive picture of the spatial and temporal organization of language processing in the human brain. Functional magnetic resonance imaging (fMRI) is the leading tool for examining the brain's activation patterns that are associated with different aspects of the language network. Electrophysiological techniques such as Event-Related Evoked Potentials (ERPs) and intraoperative brain recording studies have made possible the tracking of the temporal structure of brain activation associated with language processing (Wahl *et al.*, 2008). Advances in structural imaging techniques have provided methods for quantifying gray matter in normal and language impaired subjects, and for visualising fibre bundles that form part of the language territory in the left hemisphere (Catani & Thiebaut de Schotten, 2008). Revised guidelines for cognitive rehabilitation of acquired language disorders have been published under the auspices of the European Federation of Neurological Societies (Cappa *et al.*, 2005). These developments have not only provided the necessary diagnostic tools for examining the mechanisms of disturbed speech and language, but also have paved the way for novel neuroscience-based intervention programmes (e.g. transcranial magnetic and electrical stimulation) for the rehabilitation of individuals with speech and language problems.

#### Proposal

The ongoing research attempting to identify the genetic basis of speech disturbances and language disorders must be intensified. *FOXP2* is the first gene whose mutation or deletion is known to result in a cascade of disturbances in the brain, and in speech and language. But there are many other genes associated with neurodevelopmental disorders (such as dyslexia and autism) that need to be identified if those at risk of developing these conditions are to be helped. As genes are discovered, genotype-phenotype relationships can be elucidated, which in turn will permit the characterisation of patient cohorts. Experiments with genetically modified animals will help reveal the functions of specific genes, their downstream targets, their expression patterns in the brain and the mechanisms by which genetically transmitted speech and language problems arise. Ultimately, this knowledge will be translated into the development of effective diagnostic and neurorehabilitation techniques. With regard to acquired disorders of speech and language across the age spectrum, increased resources should be invested in several interrelated domains: (i) Considering the diversity of Europe's languages and cultures, standardised test instruments need to be developed in major European languages to characterise the components of normal speech and language, and hence to enable the identification of patient cohorts with specific types of disturbance caused by brain injury or disease; (ii) Well-equipped laboratories are needed which use standardised protocols for the different imaging tools (e.g. structural and functional MRI,

ERPs, magnetoencephalography and TMS), to systematically acquire diagnostic data on patients and to relate the imaging findings to their speech and language profiles; (iii) A Europe-wide consortium should be established to pool the imaging and language data and to compile typical profiles that describe different types of language disturbances as a function of locus and extent of brain abnormality; (iv) The availability of such convergent methodologies will generate data that can form the basis of targeted neurorehabilitation programmes for patients, and lead to evidence-based practice for clinician scientists.

#### Significance of increased research

The diversity of speech and language disorders and their brain correlates, coupled with the relatively small number of patients available in each European research centre, presently precludes systematic large-scale studies aimed at identifying mechanisms of language problems. Allocating more resources to the four domains outlined above will lead to the identification of brain mechanisms that underlie different aspects of speech and language disturbance, and help to put neuroscience at the service of neurorehabilitation. A secondary, longer-term benefit may be the development of targeted pharmacological interventions for the treatment of speech and language problems.

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### Theme I. 4: From learning and memory to long-term potentiation, synaptic plasticity and other basic cellular mechanisms

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#### Background

The mystery of memory was listed by *Science* magazine in its 125th anniversary issue (July 2005) as one of 25 major problems facing science. Memory is central to human individuality; it is our memory of past experiences that defines who we are. Losing memory is therefore like losing one's self, and many in Europe suffer neurodegenerative conditions such as Alzheimer's disease (AD), in which loss of memory is an early symptom. Others are victims of stroke, brain tumours or psychiatric disorders that attack areas of the brain involved in learning and memory. At the other end of the age spectrum, problems with the development of the nervous system can result in learning disorders, which hamper progress at school. Disorders of learning and memory have a huge financial and human cost, and to address them we need to understand how memory works. Basic research in this field draws on diverse approaches from

molecular biology to cognitive neuroscience (Colgin *et al.*, 2008). There is now a consensus that the many different types of memory are mediated by neural mechanisms that can be understood at the network, cellular, synaptic and molecular levels (Wang & Morris, 2010). One promising focus is the study of mechanisms of synaptic and neural plasticity, and the possibility that many aspects of cognitive pathologies result from specific disorders of synaptic mechanisms.

#### Past achievements in Europe

European researchers have made major contributions to this field, including: the characterisation of different forms of human memory (explicit forms, so-called because information that has been acquired earlier is later retrieved back into conscious awareness, and implicit forms, in which both the information and the processes by which it is retrieved are unavailable to consciousness but nonetheless inform behaviour); distinguishing between short- and long-term memory and describing the concept and components of working memory (Wang & Morris, 2010); the discovery of the phenomenon of long-term potentiation (LTP), and the distinct types and roles of excitatory glutamate receptors in plasticity and learning (Pinheiro & Mulle, 2008; Gardoni *et al.*, 2009); and the identification of genes (*APP*, *tau*) that are now implicated in familial forms of AD and frontotemporal dementia.

#### Proposal

It is unlikely that a single, large-scale European network or consortium would be best suited to address the outstanding questions regarding the neural mechanisms of memory. Rather, different approaches should be pursued in parallel. Top-down approaches such as those using modern brain imaging and neuropsychological techniques are guided by hypotheses about the way in which information is represented in distinct cortical areas, and how this might differ for different learning systems. Bottom-up approaches include the identification of molecules and cellular mechanisms that are activated during memory encoding, consolidation or retrieval (Triller & Choquet, 2008), and how these complex signals are computed into neural network activities relevant for learning (Colgin *et al.*, 2008). These two approaches differ both in analytic style and in their chosen subject (human, computational, whole animal *in vivo* and *in vitro*), and both should be pursued energetically. A multidisciplinary strategy is appropriate for both approaches and there are domains of analysis in which the two meet.

Networks of synaptic proteins are complex and dynamic, and their study in the context of neural plasticity and brain diseases will benefit from the development of high throughput molecular tools and nanoscopic imaging techniques through multidisciplinary efforts at the European level (Triller & Choquet, 2008). Similarly, the advancement of gene transfer methods *in vivo*, not only in rodents but also in primates, together with the development of *in vivo* imaging and ontogenetics offer great opportunities for collaboration between European neuroscientists.

In general, the field of learning and memory has been at the forefront of the emergence of methodologies that link biochemical, cell biological, genetic, morphological and physiological studies to higher brain functions. We can now envisage recording the activity of large ensembles of neurons in memory-associated brain areas, and studying the relationship between these patterns of activity and functional magnetic resonance imaging (fMRI) signals. Further advances will rely on the application of advances in physics and chemistry to complex, multilevel studies of the neural basis of learning

and memory. Efforts should also be made to improve the interaction between computational and basic neuroscientists, to provide a sharp theoretical focus to the endeavour, and to improve the management of databases and other neuroinformatics tools.

#### *Significance of increased research*

This important basic research is unlikely to command public support unless it can be shown to be delivering information relevant to the diagnosis and therapeutic management of learning and memory disorders. These disorders impact on people at all stages of life, and the ageing of the European population will result in a proportionate increase in age-related disorders such as AD. Some therapies will follow directly from increased understanding of the multiple memory systems framework, which will form the basis of rational attempts to increase the compensatory use of intact memory systems. Others will require novel pharmaceuticals to be designed on the basis of advances in our understanding of molecular mechanisms. Understanding the complex genetic determinants of memory disorders, and developing tests which allow for presymptomatic diagnosis in high risk individuals, will have a two-fold benefit: it will reassure those found not to be at risk, and it will help to identify those high risk individuals who might benefit from early medical and social interventions. Greater understanding of normal memory will have broader implications, for example in relation to education and specifically in the identification of different critical periods during development for the acquisition of different abilities (linguistic, cognitive and mathematical, to name just a few).

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### **Theme I. 5: From normal ageing to basic mechanisms of longevity**

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#### *Background*

Europe is indeed becoming the ‘old continent’. By 2050 Europe will have 173 million people aged 65 and over, which is about 28% of the total population (Database web site of the European Rural Development Project, run by the International Institute for Applied Systems Analysis). Age is the most important determinant of an individual’s healthcare needs, so the wellbeing of the elderly third of the population will largely determine Europe’s future healthcare costs. But that elderly third of the population will not only adopt the role of the retired, of consumers of healthcare services, they will also wish to lead active lives. So the general ageing of the population presents serious challenges to the basic infrastructure of our modern information society, which is largely designed for young people living in

cities. In earlier, rural societies, the elderly maintained their social status because their life experience was considered to compensate for, even outweigh, their declining capacity to assimilate new information. By contrast, even mild memory impairment can be a handicap in the modern, urban environment, where access is controlled by ever-changing passwords. Preserved cognitive ability will thus become the determining factor of successful ageing.

#### *Past achievements in Europe*

With excellent national medical records, European gerontological neuroscience is strong in population-based epidemiological studies and in the genetics of major neurodegenerative diseases. Notably, the first major breakthrough in understanding the genetics of Alzheimer’s disease (AD) was made by a European research group (Goate *et al.*, 1991). The European contribution has also been significant in understanding nutritional and hormonal influences on the ageing brain, as well as neuroinflammation, and Europe plays a key role in clinical studies on cerebrovascular and neurodegenerative diseases. It has a long way to go to catch up with the USA in research on basic neurobiological mechanisms of age-related cognitive decline, but it has made an important contribution at the level of translating basic research into clinical practice. For example, European research laid the foundations for the development of all the AD drugs that are currently available. One of the first phase II clinical trials of an amyloid-modifying drug for AD, Flurbiprofen, was led by a European (Wilcock *et al.*, 2008), as was one of the pivotal phase III trials. European groups have also led research on the development of diagnostic tools for distinguishing benign, age-related forgetfulness from early AD (Mattsson *et al.*, 2009).

#### *Proposal*

Ageing has to be considered as a normal epoch in the life of an individual, not as a disorder. However, successful ageing does not imply extended adolescence. A number of functional and even structural changes take place in the brain, which can be seen as adaptations to the prevailing environmental conditions. We need more research to understand these changes and their impact on the way the ageing brain processes information. Some changes, such as slowing of reaction times, may be a general feature of ageing nervous systems, which needs to be taken into account by those designing the environment in which we live. Others, such as problems with recent memory and focusing of attention, may result from accelerated neurodegeneration, and may be ameliorated by new drug treatments. A rational drug development process requires a better understanding of the neurobiology of the ageing brain, both at the cellular and the system level.

One serious problem with translating findings from animal models of specific neurological diseases to the elderly human population is that, in humans, those specific molecular changes occur on top of many other age-related brain changes, while most genetically engineered disease models make use of young, healthy mice. There is too little experimental research in Europe on truly aged animal models for an obvious reason: it is very expensive to maintain colonies of aged animals. By pooling European funding, we could establish such colonies to promote basic research on cognitive ageing, as is done in the USA.

The biological clock is ticking in each one of us, but its speed appears to differ from individual to individual. Environmental and lifestyle factors that set the rate of neurodegeneration warrant further research. Europe’s genetic and cultural heterogeneity should be exploited in such studies, because they provide the basis for ‘natural’

human experiments, and may compensate for the inclusion biases that have arisen in many cohort or case-control studies that have, in turn, led to disappointing therapeutic trials. There is an urgent need to improve our understanding of the interaction of genetic and environmental factors, not only in relation to neurodegeneration, but also in relation to treatment response.

An ageing population with a rapidly increasing incidence of age-related neurological disease, especially dementias, is a growing challenge to clinical neuroscientists. New, more sensitive and reliable diagnostic tools are needed to distinguish between normal ageing and age-associated pathological processes. Major research programmes are now developing disease-modifying strategies for AD, which, if successful, will require diagnostic tests capable of recognising the pre-dementia stages of AD.

Finally, the role of comorbidity in cognitive impairment in the elderly should be considered. For example, the prevalence of diabetes increases significantly with age, reaching 15–18% in the population over the age of 65. The serious vascular and neurological complications of diabetes are well known, but data on its impact on cognitive function are not clear. The nature and severity of cognitive deficits in diabetic patients seem to depend both on age and on the type of diabetes. These observations need to be investigated further in well-designed, longitudinal studies (Maggi *et al.*, 2009).

#### Significance of increased research

Dopaminergic drugs have greatly improved the lives of elderly patients suffering from Parkinson's disease, while cholinergic drugs have allowed AD patients to stay at home for longer. However, there are no pharmaceutical or other therapies available for people with 'normal', age-associated memory problems that are not related to any underlying disease.

There is a consensus on what constitutes a 'heart-friendly' diet, but no comparable diet for warding off neurodegenerative disease. Greater financial investment in research into the basic mechanisms of neurodegenerative disease, and translation of the knowledge gained into the development of new treatments, will bring long-term solutions to the growing burden of Europe's ageing population.

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## Theme I. 6: Stem cell research: from application in human disease to basic mechanisms

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#### Background

Neurodegenerative diseases, affective disorders and cerebrovascular diseases are becoming an increasing burden for Europe as the population ages. Neurodegenerative diseases cause a wide spectrum of secondary clinical disorders as a result of the chronically progressive degeneration of differentially vulnerable neuronal subtypes in the central or peripheral nervous systems. These range from muscle weakness (such as motor neuron disease and spinal muscular atrophies) to debilitating movement disorders (such as Huntington's and Parkinson's diseases (HD, PD)) and severe dementias (such as Alzheimer's and Pick's diseases). Stroke is the third most common cause of death in Europe. Affective disorders including depression are the most common brain diseases in Europe. Recent advances in stem cell research offer the hope of brain repair strategies for the treatment of these diseases.

#### Past achievements in Europe

A tremendous amount of pioneering work in the field of intracerebral transplantation of neuronal stem or precursor cells has been carried out in Europe, using PD and HD as model disorders (Lindvall *et al.*, 2004). A strong focus of European research is the tailoring of particular cellular phenotypes from embryonic stem cells for therapeutic purposes within the boundaries of European regulations (Wernig *et al.*, 2004). European researchers are starting to unravel the mechanisms and significance of neurogenesis as it occurs in the normal (Hack *et al.*, 2005) and the diseased brain of adult mammals, including humans (Höglinger *et al.*, 2004). The foundations for the study of the contribution made by haematopoietic stem cells to brain diseases have been laid in Europe (Conti & Cattaneo, 2010). However, European research in this expanding field is fragmented compared to research in the US. Integration of existing research programmes will boost European competence in this field.

#### Proposal

Research on stem cells is a promising avenue to therapeutic intervention in various neurodegenerative, affective and cerebrovascular disorders. To approach the goal of a cell replacement therapy, two strategies look particularly promising: transplantation of stem cells tailored *in vitro* and grafted into the diseased brain (Lindvall *et al.*, 2004; Wernig *et al.*, 2004), and therapeutic modulation of endogenous neurogenesis in the adult brain (Hack *et al.*, 2005; Höglinger *et al.*, 2004).

Regarding the first strategy, a detailed understanding of basic stem cell biology is needed if researchers are to control the induction of particular cellular phenotypes. In order to achieve that, it would be extremely useful to establish a neural stem cell line characterised by a high degree of differentiation plasticity, and some researchers have already attempted this (Conti & Cattaneo, 2010). A detailed comparison of the different stem cell lines already available, as well as their differentiation potential, is also needed. Genetic engineering could offer protection against the neoplastic transformation of the cells to be transplanted. The transplantation approach also needs to be refined in various ways. For example, the anatomical and functional integration of



grafts into pre-existing circuits must be improved, and we need better molecular imaging methods to monitor how the graft functions *in vivo*.

With regard to endogenous adult neurogenesis, a more detailed understanding of the factors regulating proliferation, migration and phenotypic differentiation of endogenous stem cells is required (Hack *et al.*, 2005; Höglinger *et al.*, 2004). This is best studied with stem cells grown in culture, although it must be stressed that *in vitro* properties are likely to differ from *in vivo* properties (e.g. factors promoting patterning and proliferation in the two cases). Based on such an approach, innovative strategies aimed at therapeutic manipulation of endogenous stem cells within the living brain by systemic pharmacological means (Höglinger *et al.*, 2004) or by gene therapy (Hack *et al.*, 2005) could be developed. Sophisticated tools for monitoring the behavioural consequences of these interventions *in vivo* need to be developed.

A third stem cell-based approach towards a treatment for neurodegenerative or affective disorders focuses on haematopoietic stem cells (Conti & Cattaneo, 2010). Blood-borne microglial cells derived from these cells in the bone marrow have been shown to invade the brain constitutively and in response to lesions. Due to their peripheral origin, they are accessible for therapeutic manipulation. However, their contribution to the inflammatory processes that initiate or aggravate neurodegeneration, for example, is unclear.

#### Significance of increased research

The systematic study of stem cells will potentially provide new insights, ranging from a deeper understanding of physiological brain functions to novel restorative and protective therapeutic strategies for the treatment of debilitating neurodegenerative and neuropsychiatric diseases. Tens of millions of affected Europeans stand to gain from advances towards a cell-based treatment of such disorders.

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## CONSENSUS DOCUMENT ON EUROPEAN BRAIN RESEARCH

### Chapter II: Mind-brain relationships and mental disorders

Section editor: Julien Mendlewicz

#### Theme II. 1: From mood disorders and normal mood to animal models, signalling mechanisms and genetics

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##### *Background*

The lifetime prevalence for all mood disorders is up to 20%. Unipolar depression is the most common diagnosis, showing a lifetime prevalence in women twice that for men, with a mean age at onset in the range 20–35 years. Bipolar disorder, recurrent episodes of mood elevation interspersed with depression, has a lifetime prevalence of about 2%: there is an increased risk of co-morbidity with substance abuse and anxiety disorders. Mood disorder is an unusually unpleasant experience for patients, and is the major precursor to suicide. Because of its early onset, it is also a major burden on society, expected by the World Health Organization to be the leading cause of disability in the world by 2030.

##### *Past achievements in Europe*

The classification and recognition of mood disorder has essentially European origins; the boundary between unipolar and bipolar disorder was redefined in large part on the basis of European epidemiology. In recent years, European scientists have contributed to defining the onset of mood disorder in adolescence (Tijssen *et al.*, 2010), completed cooperatively some of the largest genetic association studies to date, to establish the genetic aetiology of bipolar disorder (Wellcome Trust Case Control Consortium) and completed a successful effectiveness study (BALANCE) that demonstrates the continuing value of lithium in treating bipolar I disorder (Geddes *et al.*, 2010). The investigation of the role of stress hormones, the application of cognitive neuroscience, and the identification of appropriate biomarkers, better to define the phenotype in mood disorder have also been strongly promoted in European research centres. Advances in defining the phenotype improve the prospects for experimental medicine in psychiatry, since intermediate phenotypes such as trait differences in stress regulation, emotional processing, mood instability or cognition in combination with transcriptomic, proteomic, metabolomic and miRNomic biomarkers could inform the development of new medicines. A further promising approach for finding new drug targets is the identification of disease specific epigenetic alterations representing the molecular substrate of interactions between environmental adversity and the genome with respect to the development of mental disorders. A trans-European approach is essential in areas where expertise is distributed and the recruitment of large patient numbers or smaller samples of rare disease sub-types is desirable.

##### *Proposal*

Genetic predisposition, developmental and/or nutritional deficit, circadian rhythm disruption, early life experience, chronic stress and

drug abuse have been identified as factors contributing to vulnerability to mood disorder. Investigation of animal models must continue to play a critical part in how we understand the stress-regulating pathways of the brain and neurotransmitter systems, both monoaminergic and non-monoaminergic, that provide potential drug targets, as well as how treatments with psychotropic drugs bring about adaptive changes in those pathways (Tardito *et al.*, 2006). In addition, bipolar disorder and treatment resistant depression (TRD) are assuming increasing clinical importance but lack adequate models. In central nervous system (CNS) drug development, there is a lower than average chance of success due to the poor predictive validity of preclinical models. The introduction of human experimental medicine models at the interface between Phase 1 and Phase 2 clinical trials is the way forward in this area, to provide a rapid Go/No-Go signal, conserving resources while allowing more informed decision-making during the development process. In psychiatry the need is for standard tests of drug action analogous to those available in rodents, but applicable to humans.

In fact, human tests of emotional processing may go well beyond what is currently possible in rodents to address perceptual and cognitive aspects of emotion unique to man, such as the interpretation of the emotional content of the facial expressions of others. These are disturbed in states of illness like depression, but also in at risk subjects. More neuropsychologically informed human models could have a highly significant impact on drug development, first at the phase I/II interface as already described but second, in predicting drug response and identifying responsive sub-groups. Besides the use of specific human models, translational approaches must be further strengthened, as direct brain access is only possible in animal models. Molecular biomarker assays and epigenetics are particularly suitable for such translational research. There is a consensus that the major depression diagnosis is too broad. A better fit between drug action in the human brain and treatment response may be possible on the basis of neuropsychological measures rather than symptoms and on the basis of a combined evaluation of biomarkers and genotypes (Holsboer, 2008). This would require large scale collaboration of expert European centres that could conduct both the laboratory measures and the clinical recruitment. Finally, psychotherapy is often the preferred treatment of patients with depression, and as genomics and neuropsychology may shape physical treatments, so they may shape the choice of psychotherapies in future. There is a current need for an ambitious programme to link genetic, biomarkers, and neuropsychological and clinical measures in understanding treatment response in depression of unipolar and bipolar patients.

##### *Significance of increased research*

The progress made in the last 50 years in understanding the origins and neurobiology of mood disorders stands on the threshold of significant advances in clinical understanding. Vertical integration of basic science, genetics and clinical research is increasingly possible, and investment at each of these levels will be necessary. The objective of any clinical programme will be to improve diagnosis, prognosis and treatment of disease. Advances in genetic understanding combined

with the corresponding advances in neurocognition could now refine our currently crude diagnostic classifications and usher in an era of personalised medicine. We can now anticipate more efficient prediction of individual treatment response to psychotherapies or to medicines more tolerated and with greater efficacy. Finally, we need to reverse the long-term trend for fewer trials to be done in Europe, to increase our trial capacity. This is necessary for testing new compounds, but also for guiding patient choice between different treatments working alone or in combination.

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## Theme II. 2: From anxiety disorders, fear and avoidance to animal models, signalling mechanisms and genetics

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### Background

Disorders of anxiety include panic disorder, social and generalised anxiety disorder and post-traumatic stress disorder. Recent epidemiological studies conducted under the auspices of the European Brain Council and the European College of Neuropsychopharmacology (ECNP) show that up to 40% of the population will experience an anxiety disorder in their lifetime. Because anxiety disorders typically start early in life (the average age of the first episode is 15) and are usually both long lasting and under-treated, they represent a major burden on the individual and on society. The annual cost of anxiety disorders in Europe was recently estimated at €40 billion (Wittchen & Jacobi, 2005).

### Past achievements in Europe

European groups have contributed much to research into anxiety disorders and the development of new treatments. Teams in the UK and Switzerland worked out the molecular biology of GABA-A receptor subtypes involved in anxiety, and the first receptor subtype-selective drugs were designed in the UK and France. Pharmacogenomic approaches in mice are now being applied in a trans-European project (DEVANX), to unravel genomic and environmental vulnerability. Some of the definitive studies demonstrating the utility of antidepressants and anticonvulsants in the treatment of anxiety disorders were performed in Europe (UK, Netherlands and Germany), as were many of the key positron emission tomography (PET) and

magnetic resonance imaging studies of anxiety disorders. Moreover, the treatment of anxiety disorders with cognitive behavioural therapy was pioneered in the UK. However, although anxiety disorders are very common, they are also often comorbid with each other, with depression and with physical disorders, so finding ‘pure’ populations for study is a difficult and slow undertaking. A trans-European approach would greatly accelerate this process. To that end, a European anxiety research group – the Anxiety Disorders Research Network – has been convened, to help answer research questions and to support randomised controlled trials (Baldwin *et al.*, 2010).

### Proposal

#### Basic aspects

We need a fuller understanding of the role of neurotransmitter systems and brain circuits in the functioning of the central nervous system, their dysregulation in animal models of anxiety disorders, and their interplay with hormone and peptide neurotransmission (Gorman, 2003; Battaglia & Ogliairi, 2005). Specifically, research is required in the following areas:

1. Further characterisation of anxiety endophenotype(s) in existing animal models, and development of new behavioural and genetic animal models, will throw light on the stress-regulating systems of the brain and the neurotransmitter systems involved in anxiety, in turn revealing potential drug targets.
2. This characterisation will build on current gene association studies, and it should then be possible to create transgenic mice, which will help determine those genes’ localisation and function in the brain.
3. The involvement of pharmaceutical companies will foster the development of selective molecules targeting these gene products, and their evaluation as potential treatments in animal models.
4. New imaging (PET and single photon emission computed tomography, or SPECT) tracers based on these molecules will enable researchers to study their functional role and how it can be altered in the human brain, as possible measures of endophenotype.
5. Novel ideas about neurochemical and neurotrophic factors that change synaptic morphology and function in neuropsychiatric disorders need to be explored to provide potential new targets for drug development.

#### Clinical aspects

The key clinical research goals are:

1. To characterise the biological basis of each anxiety disorder and their overlap using imaging, challenge tests and treatment outcome studies. In addition, because of the huge cost of conducting clinical trials, it will be critical to develop procedures for testing potential new drugs in human volunteers, hence further work to develop and validate human anxiety models is required.
2. Using genetic and molecular probes, to determine the mode of action of treatments currently in use, such as the benzodiazepines and antidepressants, and to provide insights, which could potentially guide the search for novel treatments.
3. To estimate the need for, and efficacy of, long-term treatments for these disorders, with particular reference to the cost-benefit of relapse prevention versus risk of drug use and dependence.
4. To optimise the use of drug and psychotherapy treatments either alone or especially in combination, to maximise the likelihood of patients achieving full functional recovery (remission).

5. To explore ways of disrupting the aberrant learning and memory that often underpins anxiety disorders and causes it to be resistant to treatment. This is likely to involve the use of combined drug and psychological treatments.
6. To evaluate early interventions in childhood anxiety disorders and in disorders following stress and trauma, in reducing the development of chronic illness.

#### *Bi-directional collaboration and coordination*

There is generally good correlation between the findings in preclinical and clinical studies, and the two approaches have developed in an integrated fashion. However, the latest data on the efficacy of antidepressants in the treatment of human anxiety disorders have yet to be replicated in preclinical models, so their mode of action is still relatively obscure and requires further investigation at both clinical and genetic levels.

#### *Significance of increased research*

More research in this area will lead to a substantial reduction in the suffering of individuals with anxiety disorders as well as that of their families. It will also reduce the use of unsafe and unproven drugs to treat anxiety, especially alcohol and stimulants. Anxiety disorders account for a huge loss of productivity, and they also add greatly to healthcare costs as a result of unnecessary medical investigations and secondary physical illness. Reducing these would have major economic benefits for society.

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### **Theme II. 3: From addiction and normal pleasure-seeking to animal models, signalling mechanisms and genetics**

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#### *Background*

Recent data on the epidemiology of substance use disorders collected under the auspices of the European Brain Council and the European College of Neuropsychopharmacology suggest that around 25 million people in Europe suffer from one or more substance use disorder. Alcohol dependence accounts for 3.7% of those (7.2 million), illicit drug dependence 0.6% (2 million) and nicotine dependence 10% (20 million). Alcohol and nicotine dependence frequently co-occur and both disorders are responsible for severe organ damage and high levels of morbidity and mortality. Illicit drug dependence is also associated

with physical disease (such as HIV infection) and high mortality rates, especially where the drug is administered intravenously. In addition, illicit drug dependence is strongly related to criminal activities, public nuisance and high rates of incarceration. The high levels of disability, crime and public nuisance associated with substance use disorders, most of which are chronic and relapsing, constitute a serious financial burden on Europe, which has been estimated at almost €60 billion a year (Wittchen & Jacobi, 2005).

#### *Past achievements in Europe*

European contributions to the field include: the development of a large number of national and European monitoring instruments, such as the European Monitoring Centre for Drugs and Drug Addiction, which was set up in 1995; the development and testing of innovative animal models of addiction, especially for studies of vulnerability, compulsive drug-taking and relapse (Belin *et al.*, 2008); genetic research using twin registers (Vink *et al.*, 2005); animal studies using gene-expression and knockout strategies; and studies with humans combining investigation of polymorphisms with neuro-imaging. European industry has developed new, effective pharmacological treatments for addiction (such as acamprosate for alcoholism). Europe has also taken the lead in the development of harm-reduction strategies for the management of treatment-resistant addicted patients (such as medical coprescription of heroin). Most of this research has been performed in single research centres in one country. However, the relatively small effects seen in heterogeneous populations, the high levels of psychiatric comorbidity in patients with substance use disorders and the multi-ethnic nature of many European countries seriously hamper the recruitment of large population samples with acceptable levels of genetic homogeneity. A possible solution is trans-European, multicentre studies which explore the role of individual differences and genetic factors in the onset, course and treatment response of substance use disorders in different ethnic populations with sufficient genetic homogeneity.

#### *Proposal*

On the basis of animal models and neuro-imaging studies in humans, five interrelated processes have been identified to describe and explain addictive behaviours:

1. Reward (liking).
2. Motivation (wanting, incentive sensitisation).
3. Salience formation and drug-taking.
4. Habit formation.
5. Relapse.

The shift from drug use to drug addiction is marked by the change from liking and wanting to compulsive habits and, at a neural level, from ventral to dorsal striatal processes, with progressive loss of control by prefrontal executive functions. It is now timely to exploit this conceptualisation and build on recent advances in order to understand vulnerability and to develop therapeutic interventions that better target discrete phases of the addiction cycle.

The genomics of addiction encompass both inherited determinants of addictive behaviour and the effects of chronic drug-taking on gene expression. Genetic factors seem to explain 40–60% of overall vulnerability to addiction. For example, impulsivity is associated with low levels of the D2 dopamine receptor in the striatum and predicts a propensity to develop cocaine addiction and to relapse after abstinence (Dalley *et al.*, 2007). Allelic variations in several genes – for example, in dopaminergic, glutamatergic and glucocorticoid receptor genes – are likely to contribute both to behavioural traits and to vulnerability to losing control over drug-taking.

One productive area of basic research has made use of gene manipulation techniques. Gene manipulations of targets ranging from receptors to intracellular signalling pathways have been carried out, and their consequences studied at the molecular, cellular and whole systems levels. Behavioural tasks can be used to link the gene manipulation to measures of risk and addiction. Random germline mutations can be introduced into the genome at high frequency using a chemical mutagen, ethylnitrosourea (ENU), leading to the discovery of novel targets. Several large-scale ENU mutagenesis efforts are currently underway.

The key clinical questions concern the translation of basic neurobiological findings into knowledge about how the human brain functions in addiction, which can be studied using neuro-imaging techniques. This approach is already giving rise to a clearer understanding of the brain as an integrated machine with compensatory mechanisms, and to understanding of the mode of action of current treatments. It also makes it possible to calculate the cost-effectiveness of novel interventions. As new basic findings are made, the need arises to test new pharmacological and even neurosurgical (such as deep brain stimulation) interventions clinically. Finally, genetic findings may lead to genetics-based patient-treatment matching and hence more effective interventions. A key challenge is to prevent relapse and promote abstinence. Animal studies have revealed clear intermediate goals in this effort, such as targeting impulsivity and reducing the impact of drug cues on craving. They have also helped researchers to identify novel pharmacological targets which must now be evaluated in proof-of-concept studies and, eventually, in full-scale clinical trials (Lee *et al.*, 2005).

#### Significance of increased research

This research will benefit both the individual European citizen and society as a whole by reducing the suffering of patients and their families, addiction-related damage and unemployment, public nuisance due to intoxication and drug-related crime.

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### Theme II. 4: From schizophrenia and normal thinking to animal models, signalling mechanisms and genetics

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#### Background

Schizophrenia affects about 1% of the population worldwide and is characterised by severe symptoms including hallucinations, delusions,

altered motor activity (catatonia), altered emotional expression (affective blunting) and impaired ability to seek out and experience emotional gratification (anhedonia) (Andreasen, 1997). Not all the symptoms are found in the same patient and different forms of schizophrenia may exist, some of which may be difficult to distinguish from other psychoses. The estimated direct costs of caring for these patients is about €6 billion a year in Europe; the indirect costs, in terms of loss of economic productivity and crime, for example, are estimated at between €10 and 20 billion a year.

#### Past achievements in Europe

Recent years have witnessed an increased interest in schizophrenia research. In the search for the neuropathological basis of schizophrenia, for example, *in vivo* brain imaging and studies of post mortem brains have pointed to an impairment of cortical connectivity in the pathophysiology of the disease, particularly in the prefrontal and/or corticolimbic circuitry (Andreasen, 1997; Innocenti *et al.*, 2003). European research contributed to the insight that cortical misconnectivity in schizophrenia may result from the exaggerated loss and/or abnormal selection of connections in the late phases of cortical development (Innocenti *et al.*, 2003). Functional studies have pointed to underlying disorders of cortical dynamics resulting from subtle changes in cortical connectivity (Innocenti *et al.*, 2003). The search for genes specifically affected in the schizophrenic brain has identified a number of candidates (Harrison & Weinberger, 2005). The incidence of schizophrenia in the population seems to remain stable even though the disorder leads to a decrease in reproductive fitness. It has therefore been suggested by British researchers that schizophrenic disorders might be coselected with genes responsible for the lateralised structure and function of the human brain (Mitchell & Crow, 2005).

#### Proposal

Schizophrenia is to some extent genetically determined, so understanding the pathophysiology of the disease will help to clarify the interaction between genetic and environmental control of developmental mechanisms in the formation of neural circuits. Moreover, the timing of those gene-environment interactions may be critical for the phenotypic manifestation of the disease. Schizophrenia is also a developmental disorder, so with this increased knowledge it may become possible to treat or prevent it by intervening therapeutically at an age when neural circuits are still particularly plastic and capable of recovery.

To achieve this goal, different lines of research should be pursued in parallel:

1. Identify affected genes in families having a patient with schizophrenia. Several such candidate genes are currently being studied (Harrison & Weinberger, 2005).
2. Investigate the function of those genes in animal models using targeted mutagenesis and phenotyping of the models at the systems level.
3. Investigate gene-environment interactions in animals by exposing genetic models to environmental stressors at different stages of life (Fumagalli *et al.*, 2009).
4. Consolidate existing data on the neuropathology of the human schizophrenic brain by promoting the development and/or merging of European brain banks.
5. Investigate the functional circuits of the schizophrenic brain by combining imaging techniques providing high temporal resolution (electroencephalography or magnetoencephalography) with techniques providing high spatial resolution (functional magnetic

resonance imaging) and others providing high molecular/pharmacological resolution (positron emission tomography).

6. Link the results of animal studies on mutated genes to the pathophysiology of schizophrenia by analysing selected neural circuits in animals and man using comparable techniques.
7. Link genetic and brain imaging data to psychopharmacology for a more evidence-based selection of the various atypical antipsychotics. In doing so, improve the efficacy of acute and long-term treatment and prognosis.

#### Significance of increased research

Schizophrenia is a devastating condition, which touches on the relationship between brain and mind in man. Research on schizophrenia is expected to generate better diagnostic tools and early therapeutic or preventive interventions. But the implications of the findings of such research extend beyond the medical domain into the elucidation of neural circuits responsible for human cognitive functions. These in turn can be expected to generate applications in the domain of artificial intelligence and to contribute to the philosophical debate about what it is to be human.

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### Theme II. 5: From sleep disorders and normal sleep to animal models, signalling mechanisms and genetics

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#### Background

Insufficient sleep, whether induced by restriction of sleep or a sleep disorder, represents a serious risk factor for numerous conditions. Health risks include depression, coronary heart disease, diabetes and obesity, as well as mortality. Safety risks include accidents, especially in shiftwork, but also traffic accidents. The most prominent sleep disorder in western societies, insomnia, affects approximately 10% of the population chronically. Obstructive sleep apnoea is also common, with a prevalence of 4% in men and 2% in women in Europe. That prevalence is likely to increase in the future due to increased childhood obesity. The direct costs of insomnia have been estimated at \$2.5 billion a year in the US, while the indirect costs may be as high as \$100 billion a year. In 2000, traffic accidents caused by sleep apnoea alone cost \$15.8 billion and 1400 lives in the US. Corresponding estimates for Europe are currently lacking. Clearly sleep problems represent a major health and safety concern. They are also unique in that they are very common, yet remain underdiagnosed and often

untreated. It is important to clarify the mechanisms that lead to disturbed sleep, and to develop effective pharmacological and behavioural treatments for the condition.

#### Past achievements in Europe

Treating sleep disorders, as opposed to treating their symptoms, requires both basic knowledge of sleep and an insight into the pathophysiology of the disorders. Among past European achievements in basic sleep science are studies on the neurobiology of sleep (Wigren *et al.*, 2009); development of models of sleep regulation (Borbély & Achermann, 1992); molecular approaches to isolating sleep-related genes (Tafti, 2009; Dijk & Archer, 2010); and neuro-imaging studies involving functional magnetic resonance imaging and receptor imaging (serotonin, acetylcholine, GABA) (Maquet, 2005). On the clinical side, progress has been made using animal models of sleep disorders – mostly dogs, genetically modified mice and more recently the fruit fly *Drosophila*; electroencephalography (EEG) spectral analysis; pharmacological and biochemical studies; genetic studies in both single case and multiplex families; and neuro-imaging studies in patients.

#### Proposal

Genome-wide linkage and association studies, as well as sequencing of genomic DNA in well-defined population-based samples, clinical cohorts and family samples, is a potent approach for discovering single genes, networks of genes and signalling pathways that are associated with sleep regulation.

Animal models are essential for studying fundamental mechanisms of sleep regulation. While some natural animal models of sleep disorders are known, such models are lacking for important sleep disorders such as insomnia and restless legs syndrome. Studies using either constitutively or conditionally genetically modified mice can be complemented with high-throughput animal models using species whose genomes have been sequenced, such as *Drosophila*, zebrafish or the nematode *Caenorhabditis elegans*.

Sleep has been characterised and analysed using adequate EEG analysis in normal human populations, but systematic studies in different age groups and in people with sleep disorders are lacking. Environmental factors play an important role in these disorders, but that role has been largely neglected. There is an urgent need to develop structured questionnaires designed to collect reliable data on demography, medical and family history, psychological profile and life events exposure, both in patients and in matched, healthy controls. Longitudinal studies, which assess both genetic and environmental factors in sleep regulation, should be initiated, preferably using birth cohorts. The role of gene methylation and other genomic modifications (epigenetics) in sleep disorders should be investigated, both in experimental models and in humans. Complementary experiments using animal models should be conducted to investigate the effects of an enriched environment, different light-dark cycles, stressors (e.g. noise) and other environmental factors on sleep and sleep disorders.

These approaches will require collaboration and coordination between basic researchers working with animal models, others working with humans, and clinicians who can provide expertise and patients for the studies.

#### Significance of increased research

The results of this research will improve our understanding of the mechanisms by which insufficient sleep affects health, and improve the diagnosis and treatment of sleep disorders. It could also form the

basis of public health campaigns for preventing sleep disorders, aimed particularly at children and adolescents. As insufficient sleep renders people more vulnerable to a number of common diseases, preventing sleep disturbance could have a significant impact on public health in Europe – both physical and mental.

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## Theme II. 6: From eating disorders and obesity to brain mechanisms of appetite regulation

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### Background

Obesity is a major preventable cause of death worldwide. Excess weight is estimated to cause one in 13 of all deaths in Europe, or approximately one million deaths per year. Rates of obesity are increasing. Of the 77 million children living in the European Union, 14 million are overweight and will become obese adults, further exacerbating the problem. The economic cost is huge: obesity is estimated to account for up to 7% of total healthcare costs in Europe, which makes it comparable to cancer (Branca *et al.*, 2007). Eating disorders such as anorexia nervosa have a lower incidence (eight new cases per 100 000 people per year) and affect mainly young females. However, of the psychiatric disorders, they have the highest mortality rate. The aetiology of eating disorders is unknown and there is no standard treatment currently available for them.

### Past achievements in Europe

Several EU research programmes have investigated obesity and eating disorders. European researchers have described the role of peripheral hormones and central neurotransmitter pathways in regulating food intake in humans (Batterham *et al.*, 2003). Both obesity and eating disorders are multifactorial, heterogeneous diseases with a strong genetic component. However, of the more than 20 genetic disorders that result in autosomal obesity in humans, all influence the central nervous system (CNS) sensing and/or regulation of energy balance (O'Rahilly, 2009). Similarly, genes that have been shown to contribute to susceptibility to anorexia nervosa also affect the CNS (Ribases *et al.*, 2004). Food intake is regulated both by energy homeostatic mechanisms, which try to maintain a steady body weight, and by reward systems, which can override energy homeostasis.

It has been suggested that obesity reflects a drive to eat that evolved to ensure survival in periodic famines, when it was essential to accumulate body fat stores in periods of plenty. That drive persists even though we now live in an environment where high-calorie food is readily available and prolonged exercise no longer necessary. Social

and cultural factors also contribute to the development of obesity and eating disorders. Europe, with its cultural diversity and varied eating habits, provides an excellent laboratory in which to explore and identify risk factors and possible dietary interventions.

Since the discovery of leptin in 1994 (Zhang *et al.*, 1994), knowledge of the neural circuitry and neurotransmitters involved in appetite regulation has expanded enormously. Among complex behaviours, feeding behaviour is probably now the best understood at the molecular level. However, the way in which these different CNS pathways are coordinated, and how they sense peripheral signals to regulate food intake, is still poorly characterised. A coordinated network of research activities among the strongest European neuroscience groups is required to achieve that important goal.

### Proposal

Recent advances in our understanding of appetite, satiety and reward have yet to be exploited therapeutically. Research in the coming decade will further elucidate the neural circuits and neurotransmitters that are involved in obesity and eating disorders, and thus drive new therapeutic strategies, including some based on novel drug targets. Animal models must be developed, in which the physiological roles of individual genes and neurotransmitters in food intake and energy homeostasis can be investigated. *In vivo* pharmacological studies will also be important for demonstrating the efficacy of possible interventions based on the manipulation of these pathways. European researchers working on genetically modified rodents, neurogenomics, proteomics and advanced animal models must unite in a multidisciplinary, collaborative network to discover the neural mechanisms underlying obesity and eating disorders. In combination, these different approaches will help to identify new therapeutic targets for these disorders.

### Significance of increased research

Current obesity pharmacotherapy is ineffective. Bariatric surgery (e.g. gastric banding) is associated with significant mortality and economic costs, and cannot practically be applied to large numbers of obese patients. In addition, the aetiology of obesity differs between patients, therefore its treatment should be tailored to the individual patient. Research on the mechanisms underlying obesity is essential if we are to devise novel, effective therapies, which can be personalised in this way. A better understanding of the mechanisms underlying eating disorders such as anorexia nervosa will provide new avenues for therapeutic intervention.

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## Theme II. 7: From obsessive-compulsive disorder and normal carefulness and cleanliness to basic mechanisms of such personality characteristics

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### Background

Obsessive-compulsive disorder (OCD) is a chronic disorder characterised by intrusive, unwanted thoughts and ritualistic behavior that is perceived as egodystonic (alienated) to the individual. The prevalence of the disorder in the general population is about 2%, as confirmed by both European and global epidemiological studies (Sasson *et al.*, 1997). Typical age of onset is late adolescence, and both sexes are equally affected. The patient is aware that what he or she is doing does not make sense, or is extremely exaggerated (the egodystonic component of the disorder), yet feels compelled to repeat it again and again. As a result, the disorder is associated with shame and embarrassment. Typically, patients spend several hours a day engaged in these obsessive and/or compulsive behaviours, with the result that their academic achievement and productivity is reduced. Indeed, OCD is considered one of the 10 leading causes of disability.

### Past achievements in Europe

Until 30 years ago, OCD was considered a refractory disorder with an unknown aetiology. The first report of the efficacy of serotonergic medication in the treatment of the disorder came from Spain, and was later confirmed by large, double-blind, placebo-controlled studies. These studies not only established serotonin (5-HT) as a therapeutic agent, but they also showed that it played a role in the pathogenesis of the disorder (Zohar *et al.*, 1988). More recent studies point to a role for the genetic polymorphism associated with the serotonin receptor subtype 5-HT<sub>1D</sub> (Stern *et al.*, 1998), and the associated brain circuitry (Zohar *et al.*, 2004).

In spite of the impressive progress that has been made in the understanding and treatment of OCD, about 40% of OCD patients do not respond adequately to anti-obsessive medication. Considering the relatively high prevalence of the disorder in the population, conservative estimates suggest that the number of partial and non-responsive OCD patients in Europe is around one million. Although there are some promising leads as to what can be done for these patients, data are scarce. To date no trial has been conducted to look for biomarkers of the disease in a sufficiently large number of patients for whom the family and personal history are known.

### Proposal

We propose to conduct a naturalistic, open-label study in OCD patients in Europe. This will involve academically active OCD clinics – for example, those at the Universities of Florence, Amsterdam, Barcelona and Tel Aviv. With each centre providing around 100 patients, such collaboration will generate a large patient sample and thus enable us to test the predictive power of well-established biomarkers whose utility in the prediction of drug response has yet to be explored clinically. These biomarkers are: specific cognitive challenge (Chamberlain *et al.*, 2008); functional brain imaging during

symptom provocation; DNA samples; random assignment to serotonergic challenge, either with 1-(*m*-chlorophenyl)piperazine (mCPP), sumatriptan or placebo; and measures of the behavioural effects of those challenges by blind raters.

The drug-naïve patients will be evaluated on these biomarkers and then given open treatment with a selective serotonin reuptake inhibitor (escitalopram), a well-established anti-obsessive treatment, and monitored carefully. After 2 months they will be re-evaluated using the Yale-Brown Obsessive Compulsive Scale (YBOCS) as a primary measure. Drug compliance will be evaluated by means of pill counts and blood tests. There are no serious adverse effects associated with the proposed 5-HT challenge, and the transient exacerbation of symptoms that is expected to occur during it, or during the behavioural challenge (symptom provocation) given prior to brain imaging, are unlikely to differ from the symptoms the patients endure daily.

Non-responders, as defined by a decrease of < 35% in their YBOCS score, will be compared to responders (decrease of 35% or more in their YBOCS score) in terms of these biomarkers, as well as in relation to their family history of tics, OCD, other anxiety disorders, affective disorders or schizophrenia, and to their own past history of attention-deficit/hyperactivity disorder and post-traumatic stress disorder. DNA samples will also be analysed for 5-HT<sub>2C</sub>, other 5-HT receptor subtypes and dopamine markers.

### Significance of increased research

This study could help to identify the cognitive and biological basis for unresponsiveness to anti-obsessive treatment in OCD patients, as it might be expressed by differential patterns of brain activation (following an appropriate behavioural challenge) or by differential responses to a 5-HT challenge. Both 5-HT<sub>1D</sub> and 5-HT<sub>2C</sub> receptor subtypes have been implicated in OCD, and this study might help to disentangle their respective roles. Along with family and personal histories and potential differences in gene expression, the study of such variables could shed light on the subtypes and pathophysiology of non-responders. Based on this and other, similar studies, we can begin to explore alternative therapeutic approaches for those one million OCD patients in Europe who do not respond adequately to treatment. Progress in this area would in turn mean that the time from diagnosis of OCD to delivery of effective treatment that is tailored to the individual patient could be reduced, with obvious benefits for patients, their families and society at large.

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## Theme II. 8: From coma, vegetative state and brain death to mechanisms of alertness

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### Background

Up to 10% of all neurological and neurosurgical patients admitted to a tertiary care hospital suffer from diseases that lead to impairment of consciousness, coma or vegetative state (VS). Costs incurred by traumatic brain injury, the main cause of disability in young people, exceed billions of Euros per year in Europe. Impairment of consciousness is generally understood to be a dysfunction of an anatomical neural network, the ascending reticular activating system, which is responsible for arousal and maintaining alertness. This system spans a large part of the midbrain and projects to areas of the thalamus and cortex. The ascending networks exert their influence via neurotransmitters such as acetylcholine, norepinephrine, serotonin and dopamine, which, under physiological conditions, induce and maintain the activated functional state of the brain that is required for wakefulness and arousal. A decrease in activity leads to drowsiness and sleep, and damage to this system can cause a decrease in consciousness leading ultimately to VS and/or brain death.

### Past achievements in Europe

The important contribution of European researchers to this field has provided the basis for a mechanistic approach to consciousness, highlighted by the discovery of neural synchrony as a versatile code for representations in the conscious brain – both on theoretical and physiological grounds (Dehaene & Cohen, 2007). Results from European labs have helped to change the view of the thalamus from a simple gateway for sensory signals, to an active coordinator of cognitive processes whose dysfunction leads to reduced consciousness, as during epileptic absence seizures. In the 1970s, Teasdale and Jennett introduced the Glasgow Coma Scale for quantifying impairment of consciousness. Although a North American taskforce nicely summarised the medical aspects of persistent VS, European researchers published the first hints as to how to predict recovery from non-traumatic coma, post-traumatic coma and VS (Kampfl *et al.*, 1998). Further evaluation of cerebral function in coma, VS, locked-in syndrome, minimally conscious state (MCS) and brain death has been carried out by European researchers (Tshibanda *et al.*, 2010), and more recently, new definitions of syndromes of (chronic) severely impaired consciousness and, in particular, awareness, have been discussed by a European task force.

### Proposal

A Europe-wide research programme combining basic and clinical research is needed to understand the complexities of a system that, when damaged, can give rise to impairment of consciousness, impairment of wakefulness and awareness, and impairment of awareness without impairment of wakefulness (VS). We need a better understanding of the pathophysiological processes that lead to these conditions, and we need to develop therapeutic strategies that allow neuroprotective measures to be taken as early as possible to prevent secondary and/or tertiary brain damage. A concerted research effort would also lead to a streamlining of terminology and a consensus on the definitions of states such as VS, MCS and brain death.

Hypoxic brain damage and traumatic brain injury are the two main causes of impaired consciousness, coma and VS. Research is needed to enable the earliest possible correct diagnosis of hypoxic brain damage, the earliest possible estimation of the extent of a brain lesion and the earliest possible prognosis. There should be a streamlining of therapeutic approaches in emergency medicine and intensive care neurology – for example, in the use of moderate hypothermia and other neuroprotective strategies.

In terms of basic research, a multicentre project is needed to improve our understanding of the pathophysiology of impaired consciousness through the study of biochemical and inflammatory processes in traumatic brain injury and cerebral hypoxia, including studies of brain function (using functional magnetic resonance imaging) and metabolism (using positron emission tomography, single photon emission computed tomography and microdialysis) in these disease states. Specifically, such a project should:

1. Explore qualitatively and quantitatively the extent of functional impairment in comatose and VS patients using functional neuroimaging (Owen *et al.*, 2006; Monti *et al.*, 2010).
2. Prospectively study therapeutic interventions such as hypothermia, osmotic therapy and surgical decompression in patients with severe impairment of consciousness due to increased intracranial pressure.
3. Establish a Europe-wide database of long-term morbidity and mortality in patients with traumatic brain injury and hypoxic brain damage.
4. Streamline the quantity and quality of neurorehabilitation in traumatic and non-traumatic brain injury.
5. Study the impact of neurorehabilitation on the outcome for the patient, with quantitative and qualitative measurement of long-term sequelae.
6. Develop experimental animal models of traumatic and hypoxic brain injury, with particular emphasis on their validity, clinical relevance and reliability.
7. Explore the exciting possibility of using transgenic and mutant mouse models. The aim here is to study mechanisms of brain injury – mechanisms that cannot be studied in patients – and hence to provide a foundation for the development of novel therapeutic interventions.
8. Define, using better wording, the long-term condition of impaired consciousness and awareness.

### Significance of increased research

Improved acute care of patients with severe brain injury will reduce hospital and follow-up care costs. Both the individual European citizen and European society as a whole will benefit from a better understanding of the pathophysiological processes that give rise to impaired consciousness, coma and VS, and from standardisation of terminology, diagnostic and therapeutic algorithms and rehabilitation processes.

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## Theme II. 9: New vistas in violence research

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### Background

Violence and antisocial behaviour inflict a huge financial and psychological burden on society. Both produce profound changes in victims, offenders and witnesses alike. Inflicted by a small minority, violence affects the structure of society and may instigate a vicious cycle, as some victims become perpetrators (Caspi *et al.*, 2002). Effective means to break this cycle are currently few. Recent developments in neuroscience offer opportunities for more specific interventions.

### Past achievements in Europe

Genetic predispositions and adverse environments interact to increase the risk of antisocial behavior and violence during development. In addition to inherited genetic predispositions, epigenetic mechanisms – genetic malfunctions acquired during life – also have an impact on the development of violence. Such genetic and epigenetic phenomena result in important neuronal changes which in turn ‘prepare the field’ for violence-promoting environmental and social influences (Craig & Halton, 2009).

Neuro-imaging studies in humans and neurobiological studies in animals have revealed the brain structures involved in mechanisms, which result in normal manifestations of aggression being transformed into violent and antisocial behaviour (Sterzer & Stadler, 2009). Recent studies have shown that the stress hormones called glucocorticoids constitute one of the main factors that distort brain function and cause violence to surface. We know that child maltreatment and neglect are the main factors predisposing individuals to violence in adulthood (Lee & Hoaken, 2007). The emerging view is that these phenomena elicit maladaptive conflict handling and faulty stress responses, which induce important gene expression, and epigenetic changes, which in

turn bring about changes in brain circuits involved in the release and inhibition of violent and antisocial behaviour (Veenema, 2009).

Taken together, these findings shed new light on the interplay between environment, genetics and neurobehavioral events. Important details of this interplay continue to be discovered, but advances are often achieved by isolated research groups. At present, the obvious advantages that would be derived from more integrated research are insufficiently exploited in the field.

### Proposal

Recent advances in the understanding of the genetic and neurobehavioral underpinnings of violence, supported by technical advances in neuro-imaging and laboratory modelling, offer opportunities for integrating results obtained in different fields. This can be achieved by combining the multidisciplinary efforts of researchers working in those fields. Beyond advancing knowledge, such cooperative, collaborative projects would open up exciting new perspectives on effective prevention and therapy for violent and antisocial behaviour.

### Significance of increased research

European efforts have demonstrated that significant progress can be made in understanding violence and antisocial behaviour through international, multidisciplinary cooperation. The critical mass for another significant leap forward is certainly present in Europe. Now it should be a priority for the field to bring that expertise together so that the leap can be realised.

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## Chapter III: Degeneration and repair in the brain

Section editor: Manfred Westphal

### Theme III. 1: From Alzheimer's disease and other dementias to basic mechanisms of neurodegeneration

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#### Background

Dementia may affect adults of all ages, but the risk increases with age. According to European epidemiological studies, dementia affects 6–7% of the population over 65. In Europe (the European Union, Iceland, Norway and Switzerland), the estimated number of patients aged 65 and over who have dementia is 4.9 million, with an estimated annual incidence approaching one million. As Europe's population ages, these numbers are expected to increase dramatically. At present, more than half of these patients have Alzheimer's disease (AD). AD is a degenerative brain disorder that leads to decline in memory and other intellectual functions, changes in personality and behavioural disturbances. As the disease progresses, the patient becomes increasingly dependent, needing constant supervision and care. The costs related to dementia healthcare amount to €55 billion per year in Europe, most of which is spent on long-term institutional care. But importantly, this figure does not include the very high indirect costs associated with the contribution of caregivers, since the majority of AD patients live at home and are cared for by relatives and friends. AD ranks second among brain diseases in terms of the burden it places on European society (Andlin-Sobocki *et al.*, 2005).

#### Past achievements in Europe

The pathological features of AD include extracellular plaques containing beta-amyloid, intraneuronal neurofibrillary tangles containing abnormally phosphorylated tau protein, neuronal cell death, inflammatory processes, glia and microglia activation, synaptic failure and neurotransmitter disturbances (De Strooper *et al.*, 2010; Epis *et al.*, 2010). European researchers have played a major role in the genetic, neuropathological and neuroimmunological studies that have revealed the pathways underlying AD pathogenesis. Large European epidemiological studies have been crucial for mapping the medical and social risk factors of AD, as well as its preclinical symptoms. Accumulating evidence suggests that AD has a very long preclinical phase: episodic and visual memory tests can predict AD more than a decade before the clinical diagnosis, for example. European research groups pioneered the development of cerebrospinal fluid and neuro-imaging biomarkers for early disease identification and for disease modification. Finally, several European biotechnology and pharmaceutical companies, as well as university-based research groups, contributed to the basic development of novel, disease-modifying therapeutic strategies, which are now in early clinical development.

#### Proposal

Despite major progress in our understanding of the early symptoms and causes of dementia, and the development of symptomatic drugs over the last decade, the biological basis of AD is not fully understood and there is currently no cure. To find an effective treatment, we need to be able to detect the disease in its preclinical stages, in order to initiate that treatment prior to the development of the full-blown pathology. Early detection will most likely rely on a combination of novel biomarkers (based on proteomic, transcriptomic and metabonomic analyses of biological samples), neuropsychology and neuro-imaging. The validation of these techniques will require the integration of longitudinal standardised data, as well as uniform criteria for diagnosis and outcome. Better integration of basic and clinical research will also be crucial. Salient features of that integration should include:

1. A common goal of uncovering the molecular mechanisms involved in AD, especially its early stages, possibly through studies of novel animal models that recapitulate disease features.
2. The longitudinal follow-up of well-characterised patient populations.
3. A database available to all research partners, containing the biological and clinical information collected for each participating patient.
4. A neuro-imaging database.
5. A biobank and a brain bank linked to the clinical database, with protocols for standardised sampling and storage procedures, which would form the basis of correlative and biomarker studies.

These innovative, multidisciplinary research programmes should also focus on non-AD dementias, such as frontotemporal dementia, dementia with Lewy bodies, parkinsonian disorders and vascular dementia. For many of these disorders there is no treatment available today. A better understanding of the risk factors and pathogenesis of these diseases may lead not only to novel therapies, but also to the discovery of new elements in the pathogenesis of AD and to new treatment options for that disease. As new therapeutic strategies are developed, methodological research in social care, determinants of quality of life and resource utilisation in dementia should also be carried out. The European Alzheimer's Disease Consortium (EADC), established recently, is a network of 45 European centres of expertise in clinical and basic dementia research. The aim of the network is to increase the basic scientific understanding of AD, and to develop ways of preventing, slowing or ameliorating its symptoms. The EADC provides an excellent basis for the coordination of European clinical studies.

#### Significance of increased research

The rising number of people suffering from dementia represents one of the most serious challenges to healthcare systems today and in the years to come. Given that prevalence figures double in each successive 5-year age band after 65, delaying the onset of the disease by 5 years will reduce the total number of patients by 50%. So even in the absence of a definitive cure, finding a way to postpone onset of the

disease will bring substantial economic benefits. The goal of delaying the disabling symptoms and, eventually, preventing AD is feasible, and we believe that the European research community can make a significant contribution to that goal within the next decade. Their research could also have important implications for other neurodegenerative disorders, and the results obtained could form the basis of productive interactions between governments and the private sector in the form of technology transfer.

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## Theme III. 2: From Parkinson's disease and other movement disorders to the cure of basal ganglia degeneration

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### Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder whose core pathological feature is the degeneration of midbrain dopaminergic neurons associated with pathological protein aggregation. The loss of dopaminergic neurons of the substantia nigra results in impaired motor control, which produces a clinical syndrome characterised by bradykinesia, rigidity, resting tremor and postural instability. Prevalence estimates range from 66 to 12 500 per 100 000 people, and annual incidence estimates from 5 to 346 per 100 000 (von Campenhausen *et al.*, 2005). These are higher than most previous estimates, and that has implications for healthcare delivery systems. As the population of Europe ages, the costs of PD are increasing.

### Past achievements in Europe

European scientists discovered the dopamine deficit in PD and clearly lead research on cliniconeuropathological relationships in the disease. They also characterised the nonmotor symptoms of PD, which severely affect patients' quality of life, and which include cognitive dysfunction, depression, hallucinations, autonomic dysfunction, and speech and sleep alterations. These nonmotor symptoms are now measured clinically in a precise and reproducible manner (Martinez-Martin *et al.*, 2009). The cognitive dysfunction that is associated with PD may involve plastic synaptic changes in several brain areas and multiple alterations of distinct neurotransmitter systems (Calabresi *et al.*, 2006). Similar circuits may be implicated in cognitive and psychiatric abnormalities observed during pharmacological treatment. In fact, while effective for the motor symptoms of PD, dopamine replacement therapy is associated not only with adverse motor effects,

such as levodopa-induced dyskinesia, but also with adverse behavioural effects, such as impulse control disorders (e.g. pathological gambling and shopping, binge-eating and hypersexuality), punding (abnormal repetitive behaviours) and compulsive medication use. European scientists are actively involved in identifying the synaptic and neurochemical bases of these alterations (Voon *et al.*, 2009).

European researchers have also contributed significantly to the discovery of the mutations involved in familial forms of PD. Though these represent fewer than 10% of PD cases, their findings have added to our understanding of the pathogenesis of both genetic and sporadic forms of the disease. Recent rapid advances in PD genetics have revealed a prominent role for mitochondrial dysfunction in the pathogenesis of the disease, and the products of several PD-associated genes, including SNCA, Parkin, PINK1, DJ-1, LRRK2 and HTR2A, show a degree of localisation to the mitochondria (Henchcliffe & Beal, 2008). Impaired mitochondrial function is likely to increase oxidative stress and might render cells more vulnerable to this and other related processes, including excitotoxicity. The mitochondria, therefore, represent a highly promising target for the development of disease biomarkers using genetic, biochemical and bio-imaging approaches. Neuroproteomic studies have revealed quantitative changes and post-translational modifications of high abundance proteins, related to oxidative damage, confirming that deficits in energy production, protein degradation, anti-oxidant protein function and cytoskeletal regulation are associated with degenerative diseases.

The majority of animal models of PD, as well as current symptomatic pharmacotherapy, are based on European discoveries. Imaging of central nervous system (CNS) structure and function in PD is well developed and has assisted European neuroscientists in making major contributions to the development of cell replacement strategies for PD therapy, using primary dopaminergic neuroblasts.

### Proposal

Major topics that require intense research resources and effort include:

1. Standardisation of diagnostic criteria and clinical assessment tools across Europe, including procedures and algorithms for neuro-imaging.
2. The building and use of clinical, genetic and imaging databases to allow the identification and validation of biomarkers as diagnostic or prognostic tools and, in turn, to permit the identification, detailed characterisation and follow-up of large, at-risk populations. These tools will allow the detection of genes that confer susceptibility to PD and the identification of gene-environment interactions in PD pathogenesis.
3. Identification of preclinical diagnostic measures, as well as genomic and proteomic biomarkers, as a basis for early neuroprotective intervention.
4. Pharmacogenetic research to help clinicians select from the available treatments those which are most suited to particular subgroups of PD patients. Combined analysis of blood and cerebrospinal fluid biomarkers could help in this endeavour, in particular in optimising treatment specificity and sensitivity. Improved technology, in conjunction with advances in nosology and pathology, could favour the routine clinical use of biomarkers in differentiating parkinsonian disorders.
5. Development of novel, chronic animal models for basic research. At least some of these models should mimic not only the loss of dopamine in PD, but also abnormalities in other neurotransmitter systems. They should also provide information about the plastic and molecular mechanisms underlying the nonmotor symptoms of PD.

6. Identification of changes in low abundance proteins and characterisation of their functions based on protein-protein interactions and on further development of proteomic methodologies.
7. Alternative sources of cells for transplantation, since there are problems associated with the use of tissue from aborted fetuses (such as immune mechanisms leading to slowly developing inflammatory responses which may compromise long-term graft survival). The adverse event profile of transplantation must be determined, and ethical issues addressed.
8. Stem cells offer great promise as a therapy for PD, but numerous hurdles remain to be overcome in this area.
9. Deciphering the cellular and molecular mechanisms of cell death within specific cell populations in PD and experimental parkinsonism as a basis for neuroprotective interventions. In particular, the role of mitochondrial dysfunction and increased oxidative stress in the neuronal loss that leads to PD should be addressed to improve patient management and aid in the development of mitochondrial therapy for PD. The mechanisms underlying degeneration involving other cell types, such as glial cells and infiltrating immune cells, also represent promising targets for neuroprotection.
10. Identification of therapeutic proteins as well as targets for drug intervention. In particular, the role of trophic factors in the control of corticostriatal and other forms of plasticity in the basal ganglia should be analysed in experimental models of PD and other movement disorders.
11. Characterisation of the molecular mechanisms leading to L-dopa-induced dyskinesia, with the aim of blocking its development.
12. Studies of the mechanisms of the nonmotor symptoms of PD. An important aspect of such studies will be the characterisation of cortical and hippocampal circuits involved in memory, mood and olfactory abnormalities associated with the disease.
13. Development of alternative therapeutic strategies involving new medications, deep brain stimulation and gene therapy.
14. Research on atypical parkinsonian syndromes, such as multiple system atrophy and progressive supranuclear palsy, must receive special attention with respect to their aetiology, pathogenesis, diagnosis and potential therapeutic strategies, as no effective treatments currently exist for these diseases.
15. Research on the different stages of evolution of PD, to allow medication to be tailored to disease stage.

#### Significance of increased research

An increase in the quality and magnitude of preclinical and clinical research resources will establish Europe as the major global research centre for epidemiological and genetic analysis of large populations, clinical trials and drug development studies. Intensified PD research, both basic and clinical, will provide the foundations of a Europe-wide network for education and technology transfer, through which research findings can be disseminated along with well-validated knowledge on diagnosis, treatment, care and other practical information to all parties interested in PD. These include family members and care providers. The need to disseminate such information is particularly acute because of the dynamic and continuously evolving nature of knowledge about PD.

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### Theme III. 3: From stroke to basic mechanisms of post-ischæmic neuronal death

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#### Background

Acute stroke is characterised by the sudden onset of focal neurological deficits of variable nature and severity. Acute cerebrovascular diseases (CVDs) occur with an incidence of 200 cases per 100 000 people per year and are the most frequent organic disorders of the central nervous system. Their incidence increases with age. In highly industrialised countries, including European countries, stroke is the third most frequent cause of death and a leading cause of disability. Depending on the cause, acute CVDs are classified as ischaemic strokes (68–80%), spontaneous intracerebral haemorrhages (7–20%), subarachnoid haemorrhages (1–7%) and sinus venous thromboses (1–2%). The remaining 2–15% cannot be classified due to lack of data. The prognosis varies according to this classification, with intracerebral haemorrhage incurring the highest mortality. More than half of the patients remain with a severe handicap that obliges half of them to live in institutions. The cost of stroke also depends on its aetiology, with acute care estimated to cost around €22 000 per patient in Europe. That figure increases dramatically if the social costs are taken into account.

#### Past achievements in Europe

European stroke research centres have contributed a great deal to knowledge of the pathophysiology of CVDs, especially to the understanding of the development and propagation of ischaemic cell damage, and the concepts of the penumbra and therapeutic window, which are the basis for therapeutic strategies in acute ischaemic stroke. However, the only effective treatment to have been approved for acute stroke to date is the lysis of the clot obstructing the artery that supplies the affected brain region. European groups led the implementation of thrombolysis (ATLANTIS, ECASS & NINDS rt-PA study group investigators).

The concept of the stroke unit as a specialised centre for the management of acute stroke was developed in several European institutions, and together with immediate initiation of rehabilitation, forms the accepted strategy for the management of acute stroke in many European countries (Toni *et al.*, 2004). The admission to a stroke unit of a patient with acute stroke of any aetiology improves prognosis, and reduces both the length of hospital stay and mortality.

This strategy should now be taken up across Europe to ensure equal access to effective stroke care in rural as well as urban settings.

For secondary prevention of stroke after transient ischaemic attacks or minor stroke, European groups have been involved in multicentre trials of platelet-aggregation inhibitors and in evaluating the efficacy of endarterectomy for symptomatic and asymptomatic carotid stenosis (Halliday *et al.*, 2004). European neurosurgeons led the evaluation of early surgery for spontaneous intracerebral haematomas and the introduction of antithrombotic treatment for cerebral sinus venous thrombosis. Finally, European researchers have recently contributed to the critical review of past experience with clinical trials and have proposed new possibilities for the use of neuroprotective drugs (Endres *et al.*, 2008).

#### Proposal

Future research must focus on those pathophysiological mechanisms, which can be influenced by therapeutic strategies in order to prevent or mitigate the development and propagation of ischemic damage. For that purpose, it is of the utmost importance to develop models, which represent the clinical setting, and to apply investigative procedures, which permit the direct comparison of pathophysiological changes in animal models and in stroke patients. Inappropriate animal models and evaluation procedures, which cannot be applied in the clinical, setting or have no clinical correlate may have contributed to the disappointing results that have been achieved with potential neuroprotective agents to date. Fifty such drugs have produced promising experimental results but then failed to prove effective in clinical trials.

Appropriate models can be used to evaluate therapeutic concepts and treatment effects. In particular, combined pharmacological approaches should be tested in these models, such as the use of neuroprotective agents together with thrombolytics and/or hypothermia. Moreover, models of ischaemic pre-conditioning and post-conditioning could be used to translate the mechanisms of endogenous ischaemic tolerance into tools for therapeutic options. Although thrombolysis can be initiated as late as 4.5 hours after embolic stroke, only around 20% of stroke patients are eligible for this treatment, mainly due to logistical problems. In order to establish therapies for the remaining 80% of stroke patients, future research must focus on neurorestorative mechanisms after stroke, and rehabilitation. Such a research programme could generate a pharmacological or cell therapy that could be readily combined with current rehabilitative therapies. Hence, further studies of the inflammatory processes that occur in conjunction with the encapsulation of the infarct (wound healing) are warranted.

New methods for stimulating axonal outgrowth, spinal remodelling and the activation of silent and new neuronal networks are needed. Further studies are also needed to clarify whether stem cell treatment can restore brain function without risk of tumour formation. In addition, we need epidemiological studies to help us understand why the incidence of acute CVDs and their associated mortality varies across Europe, by exploring regional differences in risk factors and in stroke prevention and management strategies. Strategies must be developed to standardise diagnostic and therapeutic strategies across all European countries, and across rural and urban areas. This research will require the broad involvement of the public and the continuous education of medical personnel involved in the prevention and management of stroke.

#### Significance of increased research

Although stroke is the third most frequent cause of death in Europe, and a leading cause of disability, the funding of stroke research is a

fraction of the funding of research into cancer and heart disease (Pendlebury, 2007). The benefits of reducing the burden of stroke, for patients, those who care for them and society in general, are obvious. Such a reduction will partly depend on the basic and clinical research programmes outlined here, but also on Europe-wide coordination to ensure that all Europeans – whether they live in cities or in isolated rural areas – have access to the gold standard of stroke care.

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### Theme III. 4: From epilepsy to basic mechanisms of neuronal excitability and cell death

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#### Background

Epilepsy is a serious and common chronic neurological disorder characterised by recurrent seizures that result from abnormal synchronised neuronal discharges. As many as six million people in Europe currently have active epilepsy, and many more are at risk of developing it as a result of brain trauma or genetic defects. Epilepsy is an expensive disorder, which has major implications not only for health, but also for independent living, education and employment, mobility and personal relationships. The total European health costs associated with epilepsy have been estimated at €15.5 billion, with indirect costs accounting for more than half that (Andlin-Sobocki *et al.*, 2005; Pugliatti *et al.*, 2007). Though a large number of antiepileptic drugs (AEDs) that suppress or prevent seizures are now available, 30–40% of patients remain resistant to drug treatment. There is currently no cure for epilepsy, in the form of anti-epileptogenic drugs, nor do we have disease-modifying agents that alter the detrimental course of the disorder. We must invest in those research areas that stand to enhance our understanding of the underlying mechanisms of epilepsy and, ultimately, to generate advances in its treatment.

#### Past achievements in Europe

European epileptology centres have long occupied a leading position in epilepsy research. The most important advances to date have been: the discovery of epilepsy-related genes; the improved diagnosis of epilepsy due to better electroencephalographic techniques combined with video recording; and the use of structural and functional brain imaging for the diagnosis of epilepsy and for research.

There is now an urgent need to improve the translation of novel molecular and cellular targets identified in basic epilepsy research, into rational drug discovery processes. Multilevel *in vitro* and *in vivo* electrophysiology, genomic and postgenomic research, structural and functional brain imaging, and relevant animal models will be indispensable for identifying and testing new drug targets. These translational and multidisciplinary strategies should be supported as horizontal tools across the main research domains. The epilepsy research infrastructure, the strong European tradition in epilepsy surgery, the acknowledged skills of Europeans in phenotyping both single patients and familial cases of epilepsy, and the dense network of centres of epilepsy research excellence in Europe are the region's main assets in undertaking this research, which should be supported by European funding.

#### Proposal

It is no longer enough to try to prevent the symptoms of epilepsy. We must now attempt to cure the disease and prevent its development in at-risk patients. Research priorities are therefore as follows (Baulac & Pitkänen, 2009):

1. Improve understanding of brain development and childhood epilepsies, for example through postgenomic research on malformations of cortical development and parallel studies on surgical tissue.
2. Prevent the development of epilepsy (epileptogenesis) after brain injury, for example by exploring the genetic, environmental and other factors that predispose brain-injured patients to the disorder.
3. Translate genetic knowledge into improved patient care, for example by identifying genetic factors that increase the risk for specific types of epilepsy and the development of refractoriness to anti-epileptic drugs.
4. Reduce the life-compromising burden of seizures and epilepsy, for example by developing animal models and conducting basic research to investigate the impact of seizures on the brain's homeostatic mechanisms regulating respiratory, cardiovascular and other functions.
5. Identify the mechanisms of seizure-generation (ictogenesis), for example by identifying seizure patterns and studying the underlying mechanisms in different forms of human epilepsy using advanced neurophysiological and functional imaging tools.
6. Improve epilepsy treatments, for example by determining the epidemiology of refractory epilepsy in Europe based on prospective, Europe-wide studies of a newly diagnosed population over a number of years.

#### Significance of increased research

The research proposed will indicate ways of preventing the development of epilepsy in the large European subpopulation that suffers from epileptogenic brain insults, including stroke, traumatic brain injury and cerebral infection. In those who already have epilepsy, the research proposed could potentially generate treatments for better seizure control without adverse effects. That in turn should improve patients' chances of integrating socially, working productively and enjoying a good quality of life, with all the associated benefits that that will bring to European society as a whole.

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### Theme III. 5: From multiple sclerosis and other inflammatory disorders to basic mechanisms of neuro-immunology

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#### Background

Multiple sclerosis (MS) is a major, devastating neurological disease that affects individuals from adolescence to old age. It can present at any time, but occurs with higher probability between the ages of 20 and 40. It is a chronic, incurable disease, which occurs with variable frequency between countries, though it is most frequent in northern latitudes. The prevalence of MS in Europe is between 50 and 200 cases per 100 000 people, and approximately 700 000 MS patients live in Europe today. The impact of MS on European healthcare systems is considerable. Patients develop neurological disabilities of various types and intensities, with 10–15% requiring a wheelchair or becoming bedridden. On the other hand, around 20% maintain their professional and social activities for many years or even until the end of their lives. All MS patients require health and social support. In terms of its impact on the European economy, MS is among the costliest of brain diseases (Kobelt & Pugliatti, 2005).

#### Past achievements in Europe

In the last decade, the biggest achievement in MS research has been the development of new therapies that reduce disease activity, particularly in early stages of the disease (Aktas *et al.*, 2010). The first therapeutic agent against MS, interferon beta, came out of European laboratories, as did several of the next generation therapeutics – treatments that have already been approved or that are being tested. Underlying these therapeutic advances has been a new understanding of immune surveillance in the brain and its relation to T cell-mediated brain inflammation, concepts which were mainly developed in European labs (Wekerle, 2008). The Europe-wide programme to screen the genome for MS-related genes is the biggest and most productive initiative of its type in the world. Europeans have been involved in genetic profiling of MS brain lesions and in stem cell research in the context of repair in MS. Leading international centres for magnetic resonance imaging research in MS are located in Europe, and these have provided new insights into lesion development and its clinical representation (Franklin & Ffrench-Constant, 2008). Finally, large studies of the immunopathology of MS, which have been dominated by European researchers, have shed light on disease mechanisms and heterogeneity (Lassmann *et al.*, 2007).

#### Proposal

The inflammatory component of MS can now be treated, but no therapy exists to halt the slow accumulation of permanent functional deficit in the progressive stage of the disease. For these reasons

research efforts have to be devoted to both aspects of the disease, the immunological mechanisms responsible for inflammation and those responsible for neurodegeneration. The most pressing questions are:

1. What are the target antigens of the chronic immune response? If the auto-immune nature of the disease continues to be accepted, the question remains, is there an infectious trigger?
2. How are the inflammatory reaction and the immune response regulated in MS patients, including within their lesions?
3. What is the role of different components of the adaptive and innate immune responses in propagating brain inflammation and immune-mediated tissue damage? And can differential involvement of those components explain clinical and pathological disease heterogeneity?
4. What is the genetic basis of inflammation and neurodegeneration in the disease?
5. What are the mechanisms of tissue damage in different MS patients and do they change with chronic disease development?

All these questions must be answered if we are to develop novel therapies that either halt the disease process, halt inflammation at different stages of the disease, reduce or prevent inflammation-induced tissue injury, or stimulate repair of damaged brain and spinal cord tissue. It is unlikely that a single therapeutic strategy will achieve all these goals, rather that several different therapeutic goals will have to be targeted simultaneously in a single patient. Moreover, depending on the pathogenetic mechanisms involved, some therapies may work only in certain patient subpopulations and not in others. These research goals can only be achieved by means of a cooperative, multidisciplinary approach.

More basic research is needed to further define the mechanisms of immune surveillance, the induction and regulation of brain inflammation and the mechanisms of immune-mediated tissue injury. This will only be achieved through basic immunological and experimental studies, but the results of those studies must then be validated by investigations of disease and lesion evolution in MS patients, mainly relying on immunopathology, molecular studies of brain lesions and tracking of lesion development using innovative imaging technologies. It is expected that this basic research will generate potential new therapies whose effectiveness, mode of action and safety profile will have to be determined in experimental models. Although such models are currently available, they only capture the human disease situation imperfectly. New models of brain inflammation with MS-like central nervous system lesions must be developed, which more closely mimic the key features of the disease. Finally, new therapies will have to be tested in controlled clinical trials, using not only clinical endpoints but also an array of paraclinical disease markers. Trial design, in particular when it comes to treatment of the progressive disease, has to be optimised and the usefulness of paraclinical markers validated clinically.

#### *Significance of increased research*

Recent decades have brought considerable progress in MS therapy. For the first time, MS patients have been offered drugs that reduce the activity of the disease. However, the efficacy of these drugs is limited and on average only one third of MS patients respond well to them. For some forms of MS, such as primary progressive MS, there is currently no therapy available. Within 5–10 years, new drugs that influence the immune system more efficiently and selectively should be available. Future cell-based therapies that shape the destructive immune response and repair altered neural structures, as well as agents

that protect neurons from inflammatory damage, could reduce the suffering of thousands of MS patients.

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### **Theme III. 6: From bovine spongiform encephalopathy and Creutzfeldt-Jakob disease to prions and normal brain protein homeostasis**

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#### *Background*

Prions are cell membrane-associated proteins that can undergo conformational changes leading to self-propagation. Transmissible spongiform encephalopathies (TSE) are neurodegenerative diseases of humans and other mammalian species caused by pathogenic isoforms of prions. The most common human prion disease is Creutzfeldt-Jakob disease (CJD), which has an estimated prevalence of one to two cases per million people. Most cases of CJD are sporadic with unknown modes of transmission; a small number were transmitted by procedures involving contaminated tissues or instruments (iatrogenic CJD); 10–15% of cases are inherited in an autosomal dominant fashion (familial CJD), while a similar percentage is reported for other familial prion diseases, such as fatal familial insomnia. Over 30 mutations of prion protein have been identified in the genetic forms of TSE (gTSE) (Lovacs *et al.*, 2005). The prototype animal prion disease is scrapie, a disease of sheep and goats that has been known in Europe for nearly 250 years. Scrapie has had important implications for farmers, but the economic consequences of prion disease were brought to public attention after the diagnosis of bovine spongiform encephalopathy (BSE) in the 1980s and the emergence of the human form of BSE (new variant CJD or nvCJD) following the entry of infected beef into the food chain. Potential contamination of human biopharmaceutical products such as blood, serum constituents, cells and organs is a serious concern at present, following the report of nvCJD occurrence after transfusion of human blood products from asymptomatic cases.

#### *Past achievements in Europe*

While BSE has been reported in most European countries, the vast majority of nvCJD cases have been diagnosed in the UK. Both iatrogenic CJD and nvCJD are preventable diseases. In the past decade, regulation of the meat industry has been an important step to preventing the entry of infected cattle into the human food chain. Medical practice has also evolved, with the development of synthetic alternatives to biopharmaceuticals such as human growth hormone, and the use of appropriately sterilised or disposable surgical equipment. At present, serum products for medicinal use in the UK are procured from North American donors.



### Proposal

The common pathological mechanism underlying neurodegenerative diseases as diverse as Alzheimer's disease, Parkinson's disease and CJD is the aggregation and deposition of misfolded proteins in the central nervous system (CNS) (Forman *et al.*, 2004; Zerovnik, 2002). Therefore, understanding that mechanism has clinical significance beyond prion disease. Prion propagation is triggered by the aggregation of misfolded host protein encoded by the genome, in gTSE, or by the conformational change of normally encoded protein induced by environmentally acquired prions. Experimental animal models of prion diseases are based on direct brain inoculation of infected material. The conversion of normal prion protein (PrP<sup>c</sup>) to the protease-resistant, pathogenic isoforms (PrP<sup>sc</sup>) requires the addition of small quantities of PrP<sup>sc</sup>. The low rate of transmission in inoculation studies has led to the proposal that a second protein, called protein X, may be necessary for disease pathogenesis. But despite the limitations of such studies, the use of both *in vitro*, cell-free PrP conversion assays and chronically infected neuroblastoma cells offers an opportunity for testing potential therapeutic agents that block the conversion of PrP<sup>c</sup> to PrP<sup>sc</sup>. The cause of neurodegeneration in prion diseases is still unclear, however, and PrP<sup>sc</sup> may not be directly neurotoxic (Collinge, 2005). Future research needs to explain how misfolded proteins affect cellular homeostasis and why the CNS is so vulnerable to this disturbance. There is also a lack of knowledge regarding the duration of the pre-clinical phase of the disease. With the exception of fatal familial insomnia, familial prion diseases do not manifest clinically early in life and the incubation period of sporadic CJD is unknown. What protects the nervous system during the asymptomatic, preclinical phase and the rest of the body's systems during symptomatic neurological disease is also unknown, but the clinical manifestation of the disease may reflect the time-dependent vulnerability of specific neuroanatomical systems to protein misfolding. An important research question is how the kinetics of protein misfolding and fibrilisation are linked to age-related metabolic impairments affecting the nervous system. Normally, molecular chaperones promote normal protein folding and prevent the accumulation of misfolded proteins, which are rapidly degraded when they form inside the cell, primarily by the ubiquitin-proteasome system (UPS). The dynamic relationship between the chaperones, normally folded proteins, protein aggregates and UPS requires further research. Finally, the lack of sensitive and specific laboratory assays for TSE poses a major problem for biopharmaceutical screening (Bailey, 1999). Research in genetics and proteomics could lead to the development of signatures of human and animal prion diseases, which could be used as biomarkers. This should be considered a priority in veterinary science. Genetic screening also offers the possibility of early or pre-symptomatic diagnosis of patients and the screening of blood donors.

### Significance of increased research

Despite the considerable progress made over the past few years, fundamental questions about prion diseases still need to be answered. Most importantly, we need to know whether the infective agent is purely the PrP<sup>sc</sup> isoform of the prion protein, or PrP<sup>sc</sup> combined with some other molecule. A better understanding of prion neurobiology holds therapeutic hope for patients with common neurodegenerative disorders as well as TSE – an important goal as the population of Europe ages.

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## Theme III. 7: From head trauma to the basic mechanisms of traumatic brain damage

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### Background

Traumatic brain injury (TBI) constitutes a major health and socio-economic problem (Ghajar, 2000). It is the leading cause of death and disability among young adults, accounting for a quarter to a third of trauma deaths and for a much larger proportion of lifelong disability. Survivors of TBI frequently suffer from marked cognitive impairment, personality changes and psychiatric disturbance, which lead to a diminished quality of life. The World Health Organization has predicted that by the year 2020, road traffic accidents, a major cause of TBI, will rank third among the leading causes of the global burden of disease and injury, after ischaemic heart disease and unipolar major depression. The reported incidence of TBI in the European Union varies from 250 to 700 per 100 000 people, the incidence being higher in Eastern Europe.

### Past achievements in Europe

European groups have performed pioneering work in the monitoring and treatment of TBI, including developing the concept of secondary injury and so identifying new therapeutic avenues for limiting the final extent of TBI. French and Scandinavian groups introduced intracranial pressure monitoring, which has now become a standard of care in more severe TBI patients. Measurements of cerebral blood flow, direct measurements of brain oxygenation and microdialysis for metabolic monitoring have also been introduced by European groups (Hillered *et al.*, 2006). Guidelines for the treatment of severe TBI were developed by the European Brain Injury Consortium (EBIC) and are currently recognised as an international standard (Maas *et al.*, 1997). European groups have elucidated some complex pathophysiological mechanisms involved in TBI, research that has led to the development of various potential neuroprotective agents. Rehabilitation centres across Europe are focusing on early intensive rehabilitation, and recently a disease-specific Quality of Life scale has been introduced by European investigators.

### Proposal

Intensive, multidisciplinary collaboration on TBI is needed in Europe, involving researchers in epidemiology, basic research, neurology, neurosurgery, intensive care medicine, general traumatology, rehabilitation medicine and outcome. Population-based studies are essential if we are to accurately determine the scale of the problem, in terms of the

prevalence of TBI-related neurological disability and the indirect costs of TBI arising from long-term unemployment and care. Basic research is needed to elucidate the pathophysiological mechanisms underlying secondary damage, and to investigate the therapeutic potential of new neuroprotective agents. Some of this work can be performed in *in vitro* models, using cell cultures, but clinically relevant *in vivo* approaches will also be needed in order to recapitulate the heterogeneous clinical situation, and in which to explore the complex effects of injury on tissue perfusion, oxygenation and metabolism. An important focus of basic research should be to explore possibilities for repair by promoting regeneration and enhancing brain plasticity. A translational approach, closing the gap between clinical and basic research, may be particularly fruitful in TBI.

Europe currently has a distinct advantage over the USA in terms of stem cell research, and clear opportunities exist to increase European dominance in this field. Stem cell therapy has already proved beneficial in various neurological diseases, but research into its potential use in TBI is in its infancy. Spreading cortical depression has been identified as one of the mechanisms with pathogenic potential in TBI. Here, multidisciplinary approaches could be fruitful, as spreading depression has also been implicated in the pathophysiology of migraine and other acute brain disorders. COSBID, the Cooperative Study on Brain Injury Depolarisations ([www.cosbid.org](http://www.cosbid.org)), may serve as an example for multidisciplinary and multicentre approaches to innovative research, and deserves encouragement.

The brain's response to injury may be genetically determined, and further research in genomics, proteomics and other potential biomarkers of brain injury severity, such as the intermediate filament protein, glial fibrillary acidic protein, could shed light on individual variation in TBI, and thereby guide the implementation of more individualised treatment. There is evidence that the clinical outcome of TBI patients has improved as a result of the introduction of specialised neurocritical care centres. At the moment, however, the acute care management of TBI patients follows standardised procedures, and treatment tailored to the specific needs of individual patients is largely neglected. Very little strong evidence exists to support the various treatment or monitoring options in acute care, and further research to obtain that evidence – both for surgical and non-surgical strategies – must be considered a priority. There is little doubt about the necessity to operate on extracerebral blood clots compressing the brain, for example, but considerable debate exists over the desirability of operating on blood clots or contusions within the brain. The benefits of performing an external decompression (removal of part of the skull) to treat raised intracranial pressure after TBI are also controversial. Clinical trials are required to resolve these issues, but trials in TBI remain a methodological challenge due to the heterogeneity of the disease (Maas *et al.*, 2004).

New brain imaging techniques including perfusion computed tomography and diffusion tensor imaging are coming to maturity now. Large-scale, multicentre studies are needed to demonstrate their utility in prognosis. Magnetic resonance imaging techniques have a potentially important role in the stratification of patients for different treatment and rehabilitation strategies, though this too has yet to be demonstrated. The importance of neurorehabilitation for modifying patients' clinical outcome is increasingly being recognised. Over the last few years, specific protocols have been validated to treat not only motor deficits, but also cognitive and behavioural aspects of neurological disability. Dedicated clinical trials are needed to address these issues further.

Ethical considerations are relevant to TBI, particularly in relation to decisions to intensify or withhold treatment, and to consent to

research. Patients with more severe injuries are unresponsive and incapacitated and hence unable to provide informed consent. Researchers and clinicians alike are torn between the desire to rapidly instigate experimental therapies, and the ethical requirement to follow proxy consent procedures in situations where relatives are often unavailable (Kompanje *et al.*, 2005).

#### *Significance of increased research*

Considering that many TBI victims are young, reducing their disability is likely to have a major impact on both their and their relatives' and carers' quality of life, and on the social and economic costs of their injury.

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### **Theme III. 8: From functional brain recovery to neural plasticity, growth factors and other basic mechanisms of brain repair**

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#### *Background*

Information in the brain is stored in networks of interconnected neurons. These networks are formed during development and shaped in adulthood by neuronal plasticity, which directs the formation and maintenance of active connections and the pruning of aberrant and inactive ones (Holtmaat & Svoboda, 2009). Rearrangement of neuronal networks is required during recovery from a large number of brain diseases, from stroke and traumatic brain injury to mood disorders. On the other hand, aberrant connectivity is believed to underlie other brain diseases, including epilepsy, chronic pain and addiction. Glial cells actively inhibit neuronal regrowth, which seriously limits neuronal recovery after spinal cord injury and stroke (Maier & Schwab, 2006; Thoenen & Sendtner, 2002). Growth factors support neuronal survival and control neuronal connectivity during development and after trauma. Therefore, growth factors and their signalling mechanisms, viral vector delivery of neurotrophic genes or proteins and stem cell approaches are candidate treatments for a wide variety of brain diseases (Thoenen & Sendtner, 2002). Systemic delivery of small molecules that stimulate neurogenesis or trophic factors is an attractive therapeutic approach for the pharmaceutical industry.

*Past achievements in Europe*

The major classes of neuronal growth factors and other factors involved in neuronal plasticity and recovery have been largely discovered and characterised by European scientists and laboratories during the last two decades (Airaksinen & Saarma, 2002). The application of gene and cell therapies and neurotrophic factors with the aim of enhancing neuronal recovery has been pioneered and developed by European groups (Maier & Schwab, 2006; Lindvall & Kokaia, 2006), and these approaches are now being followed up by small biotech companies in Europe (such as NsGene, NeuroNova, AMT Biopharma, HERMA Pharma). Understanding the complex mechanisms of plasticity and repair in the brain requires multidisciplinary research and the collaboration of experts from molecular and cellular biology and developmental neuroscience to clinical neurology, neurosurgery and rehabilitation. Europe has excelled in this area and should build on these strengths. But the multidisciplinary expertise required to go forward is not available in individual member states, and the advancement of this critically important field depends on efficient collaboration and coordination at the European level.

*Proposal*

The basic mechanisms of neuronal plasticity during brain development and in adulthood, and those of brain recovery after various brain insults, need to be investigated in cell cultures and experimental animals. The potential for boosting these mechanisms by pharmacological, surgical, cellular or rehabilitation therapies, or combinations thereof, also needs to be explored. Genetics, genomics, proteomics and bioinformatics must be effectively exploited to provide new targets for therapeutic interventions. Relevant *in vitro* (cell culture, neuronal imaging, neurite outgrowth and application of genomics/proteomics) and *in vivo* model systems (discrete lesions, viral vectors, optogenetic methods and transgenic animals) should be developed and validated, which can mimic the complex nature of brain repair and plasticity and which are suitable for drug screening. Specific biomarkers or surrogate markers for brain recovery need to be identified. The molecules and mechanisms that enhance or impede brain recovery, including glial cells, extracellular matrix and trophic factors, need to be identified and their potential as therapeutic targets investigated. New growth factors for specific neuronal populations in the brain need to be identified, their signalling mechanisms characterised and the potential of either the factors themselves or their agonists/antagonists to enhance brain repair investigated. The role of neural stem cells and enhancement of neurogenesis in brain recovery also needs to be addressed.

In clinical research, the role of neuronal plasticity in the pathophysiology of, and recovery from, brain diseases needs to be better defined. The question of whether and to what extent recovery and plasticity of the adult brain can be enhanced by pharmacotherapy, cell therapy, transplantation and rehabilitation must be investigated in double blind trials, as well as how these treatment strategies could be optimally combined and targeted. The problem of delivery and targeting of substances to the brain using gene or cell therapy, controlled release substances or formulations that cross the blood-brain barrier warrants special attention. Biomarkers and imaging technologies for diagnostics and for monitoring disease progression and brain repair must be developed and validated. Recovery and reorganisation of neuronal networks is use-dependent and can only be achieved through the active participation of the patient. Therefore, effective training and rehabilitation programmes need to be combined with all therapeutic strategies and patients need to be motivated to take

part in them. Depression, which is often associated with neurological conditions, needs to be effectively treated.

Basic information about enhancers and inhibitors of recovery needs to be translated to clinical trials, and the problem of proper targeting of neuronal contacts after successful recovery needs to be addressed in both basic and clinical studies. This will require close collaboration between basic scientists of different disciplines with clinicians: neurologists, neurosurgeons, psychiatrists and specialists in rehabilitation.

*Significance of increased research*

Activation of neuronal repair and recovery is of the utmost importance following traumatic brain injury and stroke, but reorganisation of neuronal networks is a necessary component of full recovery from all brain diseases. The prospect of influencing neuronal plasticity to achieve or enhance brain recovery has enormous potential in the treatment of a large number of common, burdensome and costly brain diseases. Recent research suggests that neuronal plasticity and recovery can be influenced by rehabilitation and pharmacological treatments. Future research will be required to optimise the use of such strategies and to discover or develop new ones.

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### Theme III. 9: From brain tumours to normal mechanisms of brain cell proliferation

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*Background*

Approximately 30 000 European citizens will become ill with an intrinsic brain tumour each year. The number rises to about 54 000 if tumours of the meninges are included. As people with less aggressive forms of the disease have long survival, the prevalence of brain tumours in the European Union is about 500 000. Intrinsic brain tumours originate from the brain's glial cells, but little is known about how they are initiated. It is hypothesised that adults and children may have different tumour types due to differences in their neurons, glia and neuroglial progenitor cells (Westphal & Lassos, 2011). These tumours have a diffusely infiltrative nature and cannot be cured surgically by excision. They are also resistant to other kinds of therapy because tumour cells in the brain cannot be reached by systematically applied drugs. Almost no progress has been made in the treatment of glioblastoma, and average survival times for this disease have remained around 12 months for 60 years. The brain is considered a terminally differentiated organ with little cell proliferation or cell renewal, so a tumour can be considered a reappearance of a proliferative phenotype. Understanding the proliferation and differen-

tiation of glial cells, and these cells' interaction with stromal cells such as microglia, will also be relevant for understanding mechanisms of brain repair in other kinds of neurological disease.

#### *Past achievements in Europe*

The first neurosurgical operations for brain tumours were carried out in Europe, and the study of both the neurobiology of glial cells and of neuropathology have their roots there. In recent decades, two pivotal clinical trials that have led to new drugs for the treatment of brain tumours were coordinated in Europe, as was a study demonstrating the importance of correlative genetics (Hegi *et al.*, 2005; Westphal *et al.*, 2003). The concept of glial cell lineages and its extrapolation to gliomas was developed in Europe by Noble and Raff, as was the concept that there may be glioma-stem cells in every human glioma and that these are the basis for recurrence (Galli *et al.*, 2004). Europeans have also made major contributions to the biology of glial scarring and to advances in inhibiting glial or neuronal cell motility using repellent molecules.

#### *Proposal*

Research into brain tumours must become more integrated with the basic and developmental neurosciences. Areas of European strength in which research needs to be intensified are:

- 1 Mechanisms of glial migration. A glioma is unresectable at the time of diagnosis because of single cell dissemination. In normal development, glial precursor cells will migrate from their origin to a specific area, differentiate and then rest. If that task is not completed, apoptosis occurs, and there is massive apoptosis in the developing central nervous system. Glioma cells seem to escape that apoptotic mechanism. Two strategies for intervention are to try to reinstate it, or to harness the migratory properties of glioma cells to design attractants that will attract them back to their origin, the resection cavity, and trap them there. To achieve these goals, a coordinated research effort is needed to answer questions such as, how much do individually migrating glioma cells resemble glia or neuroglial stem cells, and is there epigenetic fixation of a migratory phenotype?
- 2 Mechanisms by which neuroglial stem cells contribute to brain repair without causing tumour formation. In injury and inflammatory lesions, scarring occurs by astrocytic proliferation, which is rapid but orderly. It prevents oligodendrocytes and neural stem cells from entering the lesions and repairing them. Some molecules have been identified which prohibit cell migration and attempts are being made to improve repair in the CNS by antagonising these. Research is needed to find out if such molecules could be of use in the glioma context, or if the glioma cell programme differs in that non-migrating cells shift to become proliferating cells. We also need to know how many types of normal stem cells there are in the adult brain, how elimination of both tumour cells and stem cells would affect a normal brain, and whether the two have different properties which would allow for selection between them.
- 3 Development of new models for brain tumour research. Research in neuro-oncology as well as in glial cell biology has made use of many *in vitro* models. However, as neuroglial interaction in the appropriate three-dimensional context is a crucial determinant of the cells' properties, organotypic or *in vivo* models are increasingly being used. The induction of angiogenesis, in particular, can only be studied *in vivo* in autotopic models. Further advances in this area will depend on research in conditional transgenics or

knockouts for neuroglial interactors or glial cell surface molecules, in which modifications in the normal biology of the brain can be studied, as well as their effects on the invasive and proliferative behaviour of neoplastic cells. Such models need to be expanded to nude mouse, severe combined immunodeficiency (SCID) mouse or nude rat backgrounds to allow for xenotransplants to be tested, as well as the recruitment of mesenchymal stem cells into the brain or brain tumours.

There is also a need for more correlative research in relation to large clinical trials and epidemiological programmes, and for a Europe-wide effort to build tissue arrays. A European Commission-funded (Fifth Framework Programme) programme for sustained drug delivery to the brain using biodegradable polymers already exists (Biodegradable Controlled Drug Delivery Systems for the Treatment of Brain Disease, coordinated by the University of Angers, France). Finally, broader, oncological questions remain to be addressed, such as what are the cell biological properties that are shared by all tumour cells.

#### *Significance of increased research*

Neurobiology and neuro-oncology are just beginning to be integrated. In the US there are now three Specialized Programs of Research Excellence (SPOREs) dedicated to glioma, which take neuro-oncological insights from bench to bedside via focused, disease-oriented, integrated research networks. Europe is strong in both glial biology and neuro-oncology, but its expertise remains fragmented. Combining that expertise will help to overcome obstacles in our understanding of the biology of brain tumours, and create novel therapeutic opportunities for this most challenging of brain diseases.

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### **Theme III. 10: From peripheral neuropathies and muscle diseases to normal function and genetics of nerve and muscle**

**T. Balta** – Patient Organization, **J.-M. Léger** – Neurologist, **R. Melcangi\*** – Neurobiologist, **U. Suter** – Neurobiologist

#### *Background*

There are more than 200 different kinds of neuromuscular disease, comprising disorders of nerves, muscles and the neuromuscular junction. Duchenne's muscular dystrophy (DMD) and amyotrophic lateral sclerosis (ALS) are archetypal examples of these devastating diseases. It has been estimated that more than one person in 3000 has a serious, disabling inherited neuromuscular disorder. The majority of patients are young and experience progressive weakness, which

eventually consigns them to a wheelchair, significantly reducing their quality of life and productivity.

#### *Past achievements in Europe*

European research groups have contributed importantly to the understanding of neuromuscular disorders. Molecular genetics studies have led to the description of numerous mutations in genes corresponding to enzymes and structural muscle proteins such as sarcoglycan, emerin and dysferlin (Nowak & Davies, 2004). Trials of promising therapies such as exon skipping and stem cell transplantation are under development in European centres (Goyenville *et al.*, 2004). Disorders of the neuromuscular junction have also benefited from research. Basic pathophysiological mechanisms, diagnostic tools and therapeutic agents have been discovered or developed in Europe (Vincent *et al.*, 2004). Regarding neuropathies, European efforts have made possible the discovery of new genes and proteins, leading to a new classification of hereditary neuropathies (Young & Suter, 2003). Progress has also been made in the study of ALS.

#### *Proposal*

Research into neuromuscular disorders would be dramatically enhanced by the creation of a European research network in this area. The mechanisms underlying neuromuscular disease include genetic, immune, metabolic and toxic processes and involve structural proteins, enzymes and ion channels. We do not know the molecular basis of many of these disorders, and to identify them we need large groups of clinically well-defined patients. Such patient groups will allow the high-throughput analysis of proteins and genes associated with the different pathologies, which in turn will lead to the identification of factors involved in disease progression. After that a series of basic studies must be conducted, including mutation analysis, genotype-phenotype correlations, identification of modifying genes and protein studies. Intracellular signalling pathways play a key role in neurodegenerative diseases such as ALS and must be studied in more depth. We also need more immunological studies to correlate disease progression with levels of auto-antibodies, cytokines, adhesion molecules and costimulatory proteins in patients' blood. Analysis of experimental models will be important too, including *in vitro* cell lines and transgenic and knockout animal models. Such basic studies will lead to the identification of new therapeutic targets.

In the clinic, it will be important to establish, coordinate and harmonise databases to create a unified resource for the definition of patient cohorts and biobanks for biological material, to which all interested research groups will have access. We also need to refine and elaborate existing clinical assessment tools, such as muscle neuro-imaging, muscle strength testing, quality of life measures and other markers of disease progression, to allow the safe and quantitative testing of new drugs in homogeneous patient cohorts. Overall, the aim will be to coordinate European basic and clinical research initiatives to promote translational research. Europe-wide epidemiological studies and multidisciplinary training programmes should also be established.

Recent results have suggested that peripheral nerves are able to synthesise neuro-active steroids and are a target for them. Indeed, they are physiological regulators, which have been shown to influence myelination and act as protective agents in different models of acquired and inherited peripheral neuropathy. Possible therapeutic interventions might be devised based on treatment with neuro-active steroids themselves, or with molecules that are able to induce their

synthesis *in situ* or that interact with their receptors (Roglio *et al.*, 2008). The promising potential of these molecules merits a sustained research and development effort.

#### *Significance of increased research*

In the last decade, many genes involved in neuromuscular disease have been identified, along with disease-related immunological and metabolic mechanisms. This has allowed precise diagnosis of patients at the molecular level, and has led to a major effort being devoted to the development of new therapies. Treatments based on stem cells, nerve transplantation technology, exon skipping and aminoglycosides, among others, promise to improve patients' quality of life and perhaps, eventually, to cure them. Selective immunotherapies based on newly discovered antigens, such as those recently found to be involved in myasthenia gravis, could alleviate patients' symptoms with fewer adverse effects than they experience now. However, a lot of research involving *in vitro* and animal models and clinical trials has to be done to refine these technologies, and to render them effective and safe for the treatment of patients with neuromuscular diseases.

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### **Theme III. 11: From spinal cord injury to basic spinal cord mechanisms**

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#### *Background*

Worldwide, around 100 000 people suffer traumatic spinal cord injury (SCI) each year. In 2005, the number of SCI patients worldwide was estimated at 2.5 million, over 500 000 of whom were in Europe. About half of SCIs are the result of traffic accidents, and more than half occur in the 16–30 age group, men being more frequently affected (60%) than women (40%) (Ackery *et al.*, 2004). SCI leads most frequently to permanent paralysis (paraplegia or tetraplegia) and a range of serious dysfunctions affecting the bladder, bowel, and reproductive and cardiovascular systems. At present, individuals with SCI must be prepared to live with their disabilities for life, and their main unmet needs, as shown in a recent European survey, are levels of occupation, sexual activity and pain relief (Kennedy *et al.*, 2006). Each year, €4 billion are spent on the management and care of SCI patients in Europe. This does not take into account the social costs of SCI, such as the need to assist the affected individual in their everyday activities or to adapt their housing to accommodate a wheelchair.

### Past achievements in Europe

In SCI, the initial impact results in a primary lesion with axonal disruption and haemorrhage leading to secondary damage mechanisms including inflammation and oxidative stress. These in turn exacerbate the pathology. The development of a number of experimental models of SCI has been central to obtaining a better understanding of the cascade of cellular and molecular events that is initiated by a traumatic event, and has allowed the definition of three different timepoints and targets, which are amenable to post-lesional interventions:

1. Reducing secondary tissue damage (neuroprotective strategies).
2. Promoting axonal regeneration (repair strategies).
3. Reactivating the central pattern generator for locomotion located in the de-afferented lumbar spinal cord (restorative strategies) (McDonald & Becker, 2003).

Many highly promising experimental interventions have been developed to promote neuroprotection and repair, but most still require significant development before they can enter clinical trials. For example, apart from early treatment with methylprednisolone, which may improve outcome after SCI in certain cases, little if any clinical progress has been made in neuroprotective strategies.

### Proposal

There is enormous potential for the further development of neuroprotective strategies, which reduce one, or more of the key mechanisms involved in secondary tissue damage, such as the recruitment of inflammatory cells to the lesion site, the expression of pro-inflammatory cytokines, or the release of prostaglandins, free radicals and cytotoxic molecules (Franzen *et al.*, 2004). Central to such research will be the clear identification of the duration of the clinical window of opportunity for the range of injury types – tailoring the intervention to acute or chronic SCI, for example, or to small or more extensive damage.

The versatility of stem cells and progenitors has led to substantial interest in the use of such cells for transplant-mediated replacement strategies (Roskams & Tetzlaff 2005). Although embryonic stem cells are in theory the most promising in this context, due to their pluripotentiality, stem cells or precursors from adult sources also require thorough investigation. Furthermore, the recruitment of endogenous stem cells to promote tissue repair promises many potential therapeutic applications.

Since severed axons often have to traverse areas of scar tissue and cystic cavitation at the lesion site, a number of tissue engineering approaches have been explored to bridge the gap, and ever more sophisticated biomaterials are contributing to this approach. The search for the ideal bridging material (based on either synthetic or natural polymers) for lesions in both the central and peripheral nervous systems will require further research. There is no doubt that it will be necessary to combine several interventions in experimental and clinical SCI, to obtain clinically satisfactory functional recovery.

The development of high-field magnetic resonance imaging (MRI) for diagnosis will allow more detailed imaging of the lesion site, as well as of any spared tissue, immediately post-injury. This technique will also prove useful in treatment follow-up, for evaluating treatment efficacy. Studies of experimental lesions and their *in vivo* correlates

using MRI will lead to better interpretation of clinical images. MRI can also be adapted for the *in vivo* tracking of cellular transplants. Although there are many experimental models of SCI, the functional analyses applied to these models still rely on the relatively subjective opinion of one or more observers, and there is a need to develop more objective, computer-assisted analytical methods.

The current clinical approach to SCI is mainly symptomatic. The only pharmacological treatment that has been approved for use in the acute phase, high-dose steroids, remains highly controversial and is often considered a treatment option rather than a standard of care. Many other drugs are being investigated for rapid clinical application, however, and some are already being tested in humans. For example, to promote outgrowth and sprouting of nerve fibres after SCI, antibodies against a very potent neurite outgrowth inhibitor, Nogo-A, have been developed and are currently in a phase I clinical trial. Initial surgical stabilisation of the spine to prevent secondary injury and pain and to permit rapid rehabilitation is currently being evaluated in a multicentre trial.

After the acute phase, treatment is chiefly based on rehabilitation: conventional physiotherapy and orthosis. Treadmill locomotor training with weight support is beneficial in paraplegic patients with incomplete SCI, but further multicentre studies are needed to refine patient selection, treatment protocols, understanding of mechanisms and complementary pharmacological interventions. More efficient prosthetic devices need to be developed for paraplegic and tetraplegic patients, and modern technology will make this possible. Certain repair strategies are in phase I trials, such as implantations of autologous, incubated macrophages.

### Significance of increased research

The enormous complexity of the neuroscientific problem posed by SCI demands input from a number of specialised research groups which are capable of bringing together effective combinations of treatment strategies in a coordinated manner. Integrated European programmes will provide the critical mass of resources and expertise needed to investigate the wide variety of animal models and outcome measures used in experimental SCI. Cooperation at the European level is also indispensable for the standardisation and optimal execution of clinical trials. Only when such trials have been completed, ensuring the transfer of new findings from bench to bedside, will Europe begin to see a diminution in the enormous financial and social burden represented by SCI.

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## Chapter IV: Revealing pain mechanisms and their control

Section editor: Jes Olesen

### Theme IV. 1: From migraine and other headaches to neurovascular regulation and basic mechanisms of head pain

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#### Background

There are more than 100 different kinds of headache. In Europe, 10% of the adult population currently suffers from migraine and 75% from tension-type headache. Of these, 10% are affected at least once a week, while 3% suffer chronic headache for 15 or more days per month. The World Health Organization has calculated that migraine is among the top 20 leading causes of years lived with disability. Migraine costs European society €27 billion per year. The cost of tension-type headache and other non-migraine headaches is similar. Almost 20% of all absenteeism is caused by headache. Women are much more affected than men, mostly during their productive years.

#### Past achievements in Europe

It is mostly European efforts that have transformed headache research into an accepted and respected branch of brain research. Europeans developed a systematic, modern classification of all headache disorders with explicit diagnostic criteria (Olesen & Steiner, 2004). Regarding migraine mechanisms, they discovered or developed:

1. Brain blood flow changes suggesting cortical spreading depression.
2. Pivotal messenger molecules such as calcitonin gene-related peptide (CGRP) and nitric oxide (NO).
3. New therapeutic agents including agonists to the serotonin receptor subtype 1 (5-HT<sub>1</sub>), called triptans, and CGRP antagonists (Olesen *et al.*, 2004).
4. The first three genetic mutations associated with migraine.
5. The first knockin mouse with increased liability to spreading depression (van de Maagdenberg *et al.*, 2004).
6. The neurobiology and imaging of pain pathways from perivascular nerve fibres in the head via brainstem to cortex (Pietrobon & Striessnig, 2003).

Regarding other headaches, they discovered or developed:

1. Pathophysiological mechanisms of tension-type headache.
2. The impact of medication overuse on headache.
3. Neuro-imaging abnormalities in cluster headache and related syndromes (May *et al.*, 1998).

#### Proposal

The ongoing search for migraine genes must be intensified and expanded to other primary headaches. It is a distinct possibility that genes for the common types of migraine, like the three already

identified for familial hemiplegic migraine, affect ion channels or membrane potentials regulating the passage of ions across the nerve cell membrane. Such mechanisms may in turn affect the release of messenger molecules. All of these mechanisms may be targets for novel antimigraine and/or headache drugs. As genes are discovered, genotype-phenotype correlations and experimental studies of headache mechanisms in genetically characterised patient cohorts, genetically modified animals and cells will become important in order to understand the genes' function.

Migraine pain originates from sensory nerve terminals around blood vessels, and tension-type headache originates from sensory nerve terminals in muscles and tendons in the head. The structure and function of the relevant pathways must be described in detail, including mechanisms of neurogenic inflammation. The conduction of painful impulses from nerve terminals via brain stem to cortex is highly regulated and, once described, offers possibilities for therapeutic intervention.

It remains unclear how migraine and other headache attacks are initiated. Known external trigger factors explain only a small proportion of attacks, and more research is needed to uncover environmental triggers and other aggravating factors. Very early mechanisms are best studied in experimentally provoked attacks, while spontaneous attacks reveal later changes. High field MRI could be applied to both spontaneous and provoked attacks to map pain processing at different levels of the central nervous system. Novel analytical methods are needed to study the associated blood and spinal fluid biochemistry. Serotonin (5-HT), NO, CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP) and ion channels play crucial roles in migraine attacks, but their targets and mechanisms of action need to be clarified, and their role in non-migraine headaches has yet to be studied. Researchers must also search for other endogenous substances that are likely to contribute to headache.

Cortical spreading depression is an established model of migraine with aura. Studies are needed to investigate how it is initiated and propagated, how it activates sensory nerves, why migraine sufferers are vulnerable to it, and whether their intermittently altered cortical excitability facilitates its induction. Different experimental models of migraine need elaboration and validation, and models of other headaches need to be developed – including ones that are amenable to high-throughput screening, such as models using genetically engineered cells. More complex animal models using neurophysiological and/or behavioural recordings are required to facilitate drug development. Last but not least, patients' priorities with regard to prevention and treatment must also be explored.

#### Significance of increased research

The advent of new migraine drugs called triptans has greatly improved the acute treatment of that disorder. Several other promising therapeutic candidates need more precompetitive development before industry shows an interest in them. No new drugs have been developed specifically for the prophylactic treatment of migraine, and

no improvement has taken place in the acute or prophylactic treatment of tension-type headache or cluster headache.

New treatments that are selective, and therefore have few adverse effects, could greatly reduce the enormous societal and personal costs of headache. More importantly, they could relieve the suffering that tens of millions of Europeans now have to endure, while at the same time increasing their working capacity and quality of life.

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## Theme IV. 2: From chronic pain and mechanisms of nociception and its control

**G. Cruccu\*** – Neurologist, **A. Dickenson** – Neurobiologist, **A. Lledo** – Industry (Eli Lilly)

### Background

Chronic pain is often defined as pain, which lasts for a prolonged period of 6 months or more. It has a detrimental effect on physical health, employment and economic status. People with chronic pain suffer on average for 7 years; one in five suffer for 20 years or more. Across Europe, chronic pain accounts for nearly 500 million lost working days each year, costing the European economy at least €34 billion. Pharmaceutical industry forecasts suggest that drug sales for chronic lower back pain alone will grow by almost 7% per year over the next decade (Eli Lilly database, 2009). Chronic pain patients suffer depression as well as problems at work and in their personal relationships. Despite advances in the management of chronic pain, many patients still suffer unnecessarily due to inadequate evaluation, assessment, monitoring and treatment of their condition. There is, as yet, no disease-modifying drug for chronic pain.

### Past achievements in Europe

Europeans contributed significantly to the modern view of pain as a complex sensory experience comprising various components. These include sensory-discriminative, emotional, and cognitive-evaluative components. The neurobiological basis of pain was first established by European neuroanatomists and neurophysiologists such as Sherrington and von Frey in the early 20th century. More recently, at the peripheral level, Europeans defined the role of capsaicin as a specific activator of pain nerve fibres, and identified the existence of silent nociceptors, as well as the correlation between nociceptive fibre activity and pain sensations in humans. European scientists played a major role in the definition of ‘central sensitisation’ during chronic pain, making

important contributions to the understanding of changes in spinal cord excitability and synaptic connectivity, and to the identification of neurotransmitters and neuromodulators in pain excitatory and inhibitory pathways (D’Mello & Dickenson, 2008; Dickenson *et al.*, 2005). They have also provided critical information about the molecular basis of nociception at all levels of the pain-processing pathways. This work has continued with the identification of novel pain receptors and channels, and with experimental pain studies in both healthy subjects and patients (Abrahamsen *et al.*, 2008; Tracey & Mantyh, 2007), where European groups are translating basic science into clinical science.

### Proposal

Progress is being made in terms of identifying the genes and molecules that participate in peripheral pain transduction and signalling, and in using them to develop genetically modified animal models and novel drugs that may shed more light on the early processing of pain (Dickenson *et al.*, 2005; Abrahamsen *et al.*, 2008). These findings now need to be applied to human pain states. In the spinal cord, a large number of neurotransmitter and neuromodulator molecules associated with afferent fibres, second order neurons, descending fibres and interneurons have been identified (D’Mello & Dickenson, 2008). Changes in the excitability and functional organisation of spinal pain pathways in developmental and pathological conditions need to be explored further, combining molecular, immunocytochemical and electrophysiological approaches in intact and genetically modified animals during acute, chronic and neuropathic pain.

Behavioural and neuronal studies are needed to investigate mechanisms and treatment of ongoing and evoked pain, and also to study the affective and comorbid changes that accompany pain. These studies should focus on pain-related regions and circuits at supraspinal levels of the central nervous system, with particular emphasis on the modulation of pain processing by affective states such as anxiety and depression. Imaging in humans and animals will contribute to our understanding of the plasticity of synaptic connections, as well as characteristics of transmission and receptor expression for different neurotransmitters. With regard to the central action of opioids, analgesia, hyperalgesia and the molecular, cellular and network substrates of tolerance and addiction warrant further study.

From a clinical point of view, there is a pressing need for tools that measure pain ‘objectively’ in humans. We distinguish five levels of ‘objectivity’:

1. Laboratory tests that use quantitative tools to measure a response.
2. Brain imaging (fMRI and PET) in humans, which has revealed the brain networks that are activated in pain and may provide an indirect way of quantifying it.
3. Quantitative sensory testing, which despite using quantitative, graded stimuli, still relies on the patient’s own evaluation.
4. Bedside examination, which relies on the physician’s experience and the patient’s ability and willingness to cooperate.
5. Pain questionnaires, which depend entirely on the patient’s evaluation (Cruccu *et al.*, 2009).

Studies are needed that combine the patient’s subjective experience, as assessed by validated quantitative and qualitative questionnaires, with objective measures provided by reliable laboratory tools. According to recent European guidelines (Cruccu *et al.*, 2009), skin punch biopsy, microneurography, laser evoked potentials and functional neuro-imaging allow the assessment of the whole nociceptive



pathway in humans, from peripheral nociceptors to cortex (Tracey & Mantyh, 2007).

#### *Significance of increased research*

Recently, both academia and the pharmaceutical industry have identified chronic pain as an important focus of their research and development efforts. A detailed understanding of pain mechanisms has enabled researchers to target central pain modulation systems at the molecular level. Methods of dose selection have improved in pain studies, and the assessment of candidate drugs in proof-of-concept studies is now easier and more cost-effective. PET competitive binding techniques have enabled researchers to determine which receptors are related to analgesia, and to identify the compounds that bind to them most efficiently. Meanwhile, fMRI and laser evoked potentials are providing a window onto central pain pathways, allowing for mechanistic targeting of potential treatments.

A better knowledge of human pain mechanisms is indispensable to the identification of specific targets for basic research, and to the development of selective and effective treatments with the capacity to relieve the suffering of millions of Europeans.

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## CONSENSUS DOCUMENT ON EUROPEAN BRAIN RESEARCH

### Chapter V: Rehabilitation, psychological care and prevention

Section Editor: Mary Baker

#### Theme V. 1: Improving life for people with brain disease: psychosocial aspects

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##### Background

It is generally accepted that around 2–3% of the population has a severe disability, which is defined as needing the assistance of another person at least once every 24 h. The cause of severe disability in the majority of cases is a brain disease, the most common being stroke, Parkinson's disease, multiple sclerosis (MS), motor neurone disease, and the after-effects of traumatic brain and spinal injuries. The overall prevalence of these diseases is around 2000 cases per 100 000 people (Langton-Hewer & Tennant, 2003). Much of the research on brain disease has naturally been directed at what causes the disease and/or to the alleviation of the impairments associated with it. However, an equally important aspect is the psychosocial problems that accompany it. For example, research on MS indicates that most of the economic burden associated with the disease is related to patients' employment problems rather than to their short-term healthcare costs (Ivanova *et al.*, 2009). The literature on traumatic brain injury (TBI) clearly shows that psychosocial problems become more apparent when an individual is discharged from hospital, and healthcare and social services begin to withdraw (Limond *et al.*, 2009). It is at that point, when most of the burden of care falls onto the family, that both the disabled individual and his or her relatives become prone to major psychological disturbances such as depression and anxiety. There is also a significant economic burden associated with caring for a disabled person.

##### Past achievements in Europe

Much of the recent research on the psychosocial impact of brain disease has been carried out in Europe. Most studies on the psychosocial impact of TBI, for example, have been conducted in the UK (Limond *et al.*, 2009). European countries have only been partially successful in providing longer-term community support for people living with disabling brain diseases; nevertheless Europe surpasses most of the rest of the world in this regard. Longer-term rehabilitation and psychosocial support is almost entirely lacking in many developing countries. Even many developed countries, such as the US, focus on short-term healthcare interventions and pay little attention to patients' longer-term needs.

It can be argued that psychosocial support mechanisms, which are crucial for improving the lives of people with brain disease, are necessarily country-specific. The support that is offered depends on the healthcare and social structure of each country, and also on government policy with regard to welfare support and financial benefits. However, Europe can learn general lessons from studies that look at the deficits in longer-term psychosocial support in different

countries, and a Europe-wide research programme would prevent individual countries from conducting repetitive research.

##### Proposal

Detailed research is needed into the problems encountered by people living with brain disease. Many studies have been conducted on the epidemiology of specific brain diseases, but surprisingly few on the epidemiology of specific symptoms. In the longer term, it is mainly those symptoms that matter to the individual, rather than his or her diagnosis. For example, we know the prevalence of incontinence associated with various specific brain diseases, but we do not know its prevalence across all brain diseases. We also have very limited knowledge of the prevalence of disabling spasticity in motor disorders such as stroke and MS. Our knowledge of sexual dysfunction and relationship problems associated with brain disease is particularly sparse (Kessler *et al.*, 2009). Simple, descriptive epidemiological studies of these disabling symptoms should therefore be regarded as a research priority. These would then inform a more coherent approach to the provision of healthcare and social services.

Another research priority should be the employment problems experienced by people with brain diseases (Khan *et al.*, 2009). Many of these diseases affect younger people who are still economically active, but our knowledge of the physical and attitudinal barriers to their employment is very limited. A better understanding of those barriers, and their reduction or removal, would open up a broader range of employment opportunities to patients, and bring about dramatic improvements in their quality of life. Similarly, our knowledge of barriers preventing people with brain diseases from taking part in leisure and social activities is virtually nonexistent at the European level, and research is needed in this area too.

##### Significance of increased research

Many governments would argue, in some cases correctly, that there have been many improvements in terms of removing physical barriers to disabled people in recent years. Public transport systems are slowly becoming more accessible to the wheelchair-bound, for example. However, physical barriers are only part of the problem. The unemployment rate among disabled people is still very high, and their participation in social activities, including leisure activities, very low. There are obvious benefits to European citizens of increasing our knowledge of these, less visible barriers, since it is only with a better understanding of them that we will be able to devise ways to reduce or remove them.

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## Theme V. 2: Improving life for people with brain disease: medical and medico-technical possibilities enabling participation in life

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### Background

Brain diseases account for 35% of the total burden of disease in Europe, and 50% of years lived with disability are a direct consequence of brain diseases (Olesen & Leonardi, 2003). Due to the ageing of the European population, further increases in disabling brain diseases can be expected. Rehabilitation, social inclusion and innovative strategies to promote the participation in life of people with brain diseases have therefore become major concerns for the European community. In a recent communication, the European Commission laid out its policy priorities with regard to ensuring that able-bodied and disabled people enjoy equal opportunities across the European Union (European Commission, 2003).

### Past achievements in Europe

Research in the basic and clinical neurosciences has led to the alleviation of many of the disabling symptoms of brain disease, enhancing chronically ill patients' ability to participate and greatly improving their quality of life. New pharmacological therapies are also in development. Research into rehabilitation has led to a wide range of skills training techniques, such as constraint-induced therapy, which are designed to improve such patients' ability to function day-to-day. Psychotherapy, neuropsychological and psychosocial skills training, speech therapy, physiotherapy and occupational therapy also increase participation by restoring a patient's skills. Assistive technology has helped where patients are disabled and complete rehabilitation is not possible. Wheelchairs, walking aids and electrical mobility devices have greatly enhanced the mobility of many disabled people. Environmental control systems have been developed that reduce severely disabled patients' dependency on carers, and even enable them to communicate (Craig *et al.*, 2005). Neuroprostheses that work through functional electrical stimulation of the brain can improve motor function (e.g. grasping), autonomous function (e.g. micturition, ejaculation) and sensory function (e.g. hearing, seeing), enhancing an individual's independence (Nelles, 2004). Other advances that have improved disabled patients' participation in life are new languages for the blind and deaf, and the integration of these languages into information technology. European centres have contributed significantly to the development of brain-machine interfaces, which transform brain activity into signals for controlling external devices

and enable severely disabled individuals to interact with their environment (Pfurtscheller *et al.*, 2003).

### Proposal

Assistive technology plays an important role in enhancing disabled people's participation when medicine can only promise partial recovery. This is an area of great innovation, but new technologies are often expensive, and they need to be tested for both efficacy and cost-effectiveness. The cooperation of designers, engineers, clinicians, industry representatives, users and policymakers will be necessary to make these innovations accessible to the disabled population. Mobility devices as apparently simple as wheelchairs still need improving, because while effective, user-friendly wheelchairs promote participation, ineffective ones represent a barrier to it. Assistive devices for personal care, communication, sensory function, and for managing and coping with cognitive disorders, must be developed further. Environmental control systems also need refining to ensure that they meet individuals' needs. More attention should be paid to the special needs associated with specific disabilities, such as the orientation and navigation problems of the visually impaired, and the communication difficulties of aphasic and deaf people. Research is also needed to ensure that disabled people have access to the information society ('eAccessibility'), as well as to transport systems and public buildings. Computer adaptation technologies and software such as automatic speech recognition programmes need further development, as do systems for integrating multiple assistive devices.

Overcoming disability goes beyond merely complementing the individual's deficits with assistive technology, however. It often requires a mix of mainstream and assistive technologies. Rapid changes in the mainstream technological environment can exclude disabled people, and technical innovations that take a wide range of disabilities into account should be promoted. Social exclusion and its causes should also be studied in disabled populations. The contribution of disabled people themselves to such research, and to the design of solutions, will be essential for the construction of a truly inclusive society.

### Significance of increased research

Research on these issues will improve quality of life for disabled individuals who experience barriers to participation in social and economic life, enabling them to live fully, independently and according to their individual needs and preferences. By encouraging equal opportunities for disabled people, European society will benefit by seeing greater numbers of people participating in social affairs and in the workforce, and from a concomitant reduction in the social and economic burden of disability.

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### Theme V. 3: From physical, occupational and speech rehabilitation to plasticity of the motor coordination and speech systems

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#### Background

Motor and cognitive dysfunction after common neurological disorders such as stroke, traumatic brain injury (TBI) and neurodegenerative diseases represents an enormous burden of disability. About a quarter of stroke survivors are unable to walk, for example, while one third have persistent aphasia. At least a quarter of survivors of severe TBI are affected by memory impairment. The role of pharmacological treatments in promoting recovery from neurological damage remains limited, even if research is suggesting new therapeutic opportunities in the potentially beneficial association of drug therapy and rehabilitation. As a consequence, the development of effective, nonpharmacological treatments could have a significant impact on the burden of disability caused by neurological damage.

#### Past achievements in Europe

For many years, the field of rehabilitation has been characterised by largely empirical treatments, which make limited reference to the basic science of neurological recovery. Furthermore, the quality of studies devoted to the assessment of the efficacy of rehabilitation methods has been quite low, resulting in general uncertainty about the evidence-based efficacy of many nonpharmacological treatments. However, the situation is changing rapidly due to the increased interest of basic neuroscientists in recovery and rehabilitation. It is becoming increasingly clear that any development in this field is likely to result from a better understanding of the neural mechanisms responsible for plastic changes in the brain, and of the effects of training and other environmental influences on those mechanisms.

#### Proposal

In the case of the rehabilitation of motor and cognitive disorders resulting from stroke, several promising lines of investigation have opened up. These include the use of functional imaging methods, particularly functional magnetic resonance imaging (fMRI), to assess the effects of specific treatments on cortical reorganisation. Besides the basic research interest that such studies hold, there is a hope that their findings could guide decision-making about the type and duration of interventions to be assessed in clinical trials.

Recent data on the use of transcranial magnetic stimulation or noninvasive cortical stimulation to maximise cortical plasticity and enhance the efficacy of training interventions (Miniussi *et al.*, 2008) are in need of replication and extension. There is also increasing interest in the application of theoretically-driven approaches to rehabilitation, such as constraint-induced movement and language therapy, and errorless learning procedures for the management of cognitive disorders. Other promising techniques include the use of virtual reality (Kim *et al.*, 2009) and interactive robotics (Takahashi *et al.*, 2008) for training in motor skills.

Dementia is fast becoming one of Europe's healthcare priorities. Nonpharmacological treatments in this area are aimed at reducing the disability that is associated with progressive neurological dysfunction. There is evidence that cognitive stimulation approaches are cost-effective in people with dementia (Knapp *et al.*, 2006). Another crucial area of investigation, which can be approached only within a multidisciplinary framework, is the combination of pharmacological

treatments with training and rehabilitation techniques. Pilot studies have been conducted in the context of motor and language disorders, as well as in dementia, with promising results (Berthier *et al.*, 2009), but again these need to be replicated and extended.

#### Significance of increased research

The potential impact of effective nonpharmacological treatments on the burden of functional disability following common neurological disorders such as stroke and dementia is enormous. For example, any intervention, which significantly accelerated motor or language recovery in a substantial proportion of patients, would have an impact on the length of hospital stay and on the quality of life of long-term survivors of cerebrovascular disorders. Similarly, any gain afforded by behavioural interventions in patients affected by early Alzheimer's disease, at the level of functional autonomy, would result in improved quality of life, reduction in caregivers' burden and delayed nursing home admission for these patients.

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### Theme V. 4: Prevention of brain diseases and trauma

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#### Background

One third of the European Union's population is affected by a psychiatric disorder each year, and those affected are almost twice as likely to die as healthy individuals. Even in depressed patients, less than half of this increased mortality can be explained by higher suicide rates. Dementia affects almost 5 million people in Europe, and stroke 6 million. Their prevalence will substantially increase in coming years, as the population ages. Epilepsy affects 3.4 million people in Europe, and Parkinson's disease (PD) more than 1 million (Witchen & Jacobi, 2005). Almost all brain diseases are characterised by a chronic course with either multiple episodes and a partial remission between episodes (as in major depression and bipolar disorder) or a continuous chronic evolution (as in schizophrenia, dementia, PD and epilepsy). Many start in adolescence and their burden and cost arise both from the direct impact of the disease and to its more indirect effects on education and social skills learning (Andlin-Sobocki *et al.*, 2005). Suicide is associated with some brain diseases. In developed countries, more than 90% of suicides are committed by individuals with at least one psychiatric diagnosis, and the majority have more than one. The lethality of suicide attempts has been shown to be

positively correlated with the number of brain diseases a person has, both in the US and in the EU (Lecrubier, 2001).

#### *Past achievements in Europe*

There have been no large, Europe-wide epidemiological studies of brain diseases. Methods, definitions and sample sizes differ from country to country. A proper evaluation of the needs of patients, and identification of at-risk or high-cost groups, is missing, which makes it difficult to make decisions about the allocation of resources. The awareness and evaluation of major risk factors such as hypertension for stroke and lifestyle for substance abuse varies enormously from country to country. Despite the high prevalence and burden of brain diseases, recognition and treatment remain poor, especially in primary care structures (Tylee *et al.*, 1999). Little is known about the real value of treatment for these chronic diseases, since most data are provided by industry at an early phase of treatment development, for regulatory purposes. Crucial information is missing as to how these very chronic patients should be treated, the long-term benefits of treatment, and how to identify subgroups associated with different, long-term outcomes. Preliminary data suggest that for many brain diseases, early intervention is associated with modification of the course of the disease and/or a better outcome. Research on diagnostic tools and criteria that could improve the early identification of the disease is lacking for schizophrenia and Alzheimer's disease (AD). Cohorts of patients that have been identified and treated early vs. later are not available, so it is not possible to assess the preventive impact of early treatment. Little is known about how the organisation of care, psychosocial factors and lifestyle affect the prevalence and outcome of brain diseases.

#### *Proposal*

Large, international epidemiological studies with a common methodology are needed to improve basic epidemiological knowledge (such as how the stroke population breaks down by age group, gender and country), to identify at-risk groups who may be amenable to intervention and prevention, and to improve criteria for triggering therapeutic or preventive interventions, especially when those criteria differ from diagnostic criteria (as in AD, schizophrenia and stroke). High and low prevalence brain diseases should be studied separately.

Early identification of brain diseases or of major premorbid/prodromal features is a major challenge in many different brain diseases, especially where prevention of the disease or the effects of disease-modifiers are to be assessed. Early diagnostic and prognostic markers must also be refined to facilitate studies on neuroprotection and how this affects the outcome of psychosis. Research is needed to assess whether the early treatment of anxiety disorders prevents the development of later comorbid conditions such as depression, limiting the long-term burden and cost associated with those conditions.

Long-term pharmaco-epidemiological studies are needed to better define the benefits of treatment and what factors (personal, environmental, and factors specific to the intervention) predict outcome. There should also be more research to improve recognition, treatment and pathway-to-care for brain disease patients, which in turn will enable primary care and psychosocial support systems to be assessed and improved. Such studies could benefit from the diversity of healthcare systems and expertise available in different European countries, provided that data are collected according to identical methods and definitions.

The association between brain diseases and other diseases is much higher than chance. For example, in myocardial infarction major outcome predictors are the ventricular ejection fraction and the existence of depression. Multidisciplinary studies are needed to

explore the causes and consequences of this high comorbidity, while other studies should investigate large populations at risk of suicide (perhaps starting with those with more than one psychiatric diagnosis), to identify the best therapeutic and healthcare strategies for preventing this rare but devastating event.

#### *Significance of increased research*

The potential benefits of such a research programme include:

1. Reducing a major burden of disability experienced by a very large proportion of the EU population.
2. Decreasing the prevalence and hence the cost of diseases that are currently responsible for about one third of total medical costs in Europe, as well as very high indirect costs resulting from lost productivity.
3. Decreasing the mortality associated with brain diseases.
4. Developing industry and social services in a major economic domain.
5. Identifying relevant subgroups with specific risk factors, treatment responses and/or treatment outcome. This will also be valuable for those working in other research areas such as neurobiology and genetics.

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### **Theme V. 5: Ethics**

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#### *Background*

The relationship between mind, brain and body has been analysed throughout history, but the tools available to modern neuroscience mean that descriptions of neuronal and cognitive processes are constantly being refined, that both brain diseases and 'normal' brain function are being redefined (Merskey, 1986), and that new technological possibilities for manipulating the brain are opening up. These developments have profound ethical implications. Though they stand to benefit mankind, their application and dissemination must be carefully controlled so that neither individual autonomy, nor human dignity, nor a person's right to privacy are violated in the process.

#### *Past achievements in Europe*

According to the Declaration of Helsinki (World Medical Association, 1964) and the Oviedo Convention (Council of Europe, 1997), in conducting medical research on human subjects, scientists should place considerations relating to the wellbeing of the human subject above the interests of science and society. This means that a balance of

treatment must be maintained to protect life while avoiding unreasonable therapeutic demands from the patient or family. The treatment of vulnerable patients, particularly children and elderly people, is an area that is fraught with ethical problems. Living wills and advance directives are now used in Europe, as elsewhere in the world, but as chronic brain diseases become more prevalent, end-of-life decisions and the use of these directives will become more relevant and complex. Despite these complexities, clinicians must continue to ensure patient autonomy while providing appropriate and adequate treatment.

#### *Proposal*

Scientific results need to be communicated effectively to the public, but careful attention must be paid to the proper management of expectations regarding therapies. Advances in human brain research must not become tools for social control of medicines, for manipulating human behaviour or for social discrimination. Urgent consideration is needed as to whether ethical limits should be imposed on potential technological manipulations of the brain, if those manipulations lead to the enhancement or substitution of cerebral functions, and if so, what those limits should be.

Animal experimentation is necessary, both for developing scientific knowledge and to avoid performing potentially harmful experiments on human beings, but scientists must recognise that differences between humans and animals also mean that limits and conditions should be imposed on the use of animals (Frey, 1980). Even though animals have few rights of their own, they should not merely be regarded as biological material. Scientists must balance the objectives of a research programme with the need to afford the animal the protection that it requires, in order to prevent needless suffering.

In both the experimental and the therapeutic fields, we need to find a way to obtain proper informed consent from, or on behalf of, patients with brain diseases, who are often not competent to provide it. It is also necessary to identify the ethical boundaries to living wills. A living will must neither limit a doctor's autonomy nor include any requests for interventions relating to euthanasia. In psychiatry, there are cases where the physician has the power to

remove the patient's rights and liberty without that patient's consent. This power may be exercised even though the patient may have committed no offence or misdemeanor, and is an exception to the general rule of law in all civilised societies. Such power should be exercised sparingly and with due regard to the patient's dignity and clinical needs.

#### *Significance of increased research*

There is a pressing need to address ethical issues raised by basic and clinical research in neuroscience. The primary objective should be to never separate the wish to cure disease from the need to care for individual patients. It is also necessary to create the ethical and cultural conditions in which we can remove or at least reduce the stigma attached to brain diseases.

As long as our understanding and treatment of brain diseases advances, and we continue to monitor the appropriateness of treatments and pain therapy, while bearing in mind the patient's need for social integration, the quality of life of patients with brain disease can only improve. This approach is a matter of justice and human rights, as defined by the Convention on the Rights of Persons with Disabilities (New York: United Nations, 2008), and by following it we will ensure that human dignity is preserved.

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## Chapter VI: Sensory systems and autonomic disturbances

Section editor: Renato Corradetti

### Theme VI. 1, 2, 3: Disturbances and diseases of sensory system

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#### Background

Impairment or loss of one or more senses is relatively common and the consequences range from difficulties in social and working activities to severe physical and/or psychological handicaps. Although rarer than other nervous system pathologies, sensory disturbances represent a substantial economic burden that is probably underestimated and is often not taken into consideration in statistical assessments of healthcare costs. For example, severe to profound hearing loss affects 1 in 1000 newborns, another 1 in 2000 children before they reach adulthood, and 60% of adults over 70. Hereditary retinal degeneration has an incidence of 1 in 4000, while age-related macular degeneration (AMD) affects 18% of those over the age of 85 in Europe, and approximately 10% of those aged between 75 and 84 (Vingerling *et al.*, 1995). The incidence of these disorders is growing rapidly due to increasing life expectancy. Smell and taste disorders are common, yet little is known about their nature or causes. It is increasingly evident that disturbances of one or more sensory pathways are involved in the symptomatology of brain diseases including Parkinson's disease, dystonia, autism, schizophrenia and migraine.

#### Past achievements in Europe

Europeans have been at the forefront of research into sensory disorders, especially in elucidating the genes and pathophysiological processes involved and, in the case of vision, in understanding the proteins that are expressed in the retina. In recent years the European Commission (EC) has promoted investigation into pathological states affecting vision at different levels, from the retina to the visual cortex, through dedicated funding of cooperative projects such as EVI-GENORET, AAVEYE, EuroV1sion, CRUMBS IN SIGHT and RETICIRC, under the Sixth and Seventh Framework Programmes. Similarly, the EC has supported networking to develop new screening strategies for hearing loss in the elderly (AHEAD III), and funded a large Integrated Project, EuroHear, to study the development of the inner ear and identify the molecular mechanisms of hereditary hearing impairment.

#### Proposal

Increasing our knowledge of the physiology of sensory systems will lead to the identification of new therapeutic targets for the treatment of sensory alterations that are secondary to disease and/or ageing. We do

not fully understand the physiological mechanisms of the six senses (sight, touch, hearing, smell, taste and the perception of self-movement), and it is only recently that the molecular basis of the mechanical sensations of touch and hearing has been elucidated. Investigation of animal models will continue to play a critical role in how we understand sensory pathway organisation and plasticity, from the peripheral detection of sensory stimuli to their organisation into cortical maps and integration into behavioural adaptation to the environment. For example, the barrel cortex has yielded a wealth of information about cortical plasticity in recent years. It is one of the few cortical areas studied so far in which plasticity can be examined from birth through to adulthood. Similarly, studies in animal models will help researchers to identify the role of genetic factors in establishing physiological functioning in each of the six sensory systems, as well as that of neurotrophic factors, neurotransmitters and neuromodulators. This in turn will contribute towards a fuller understanding of the genetic, developmental and postnatal causes of, for example, deafness and blindness that are not related to infectious or traumatic injuries, and will lead to a better understanding of sensory function in general. Novel ideas about neurochemical and neurotrophic factors that change synaptic morphology and function in sensory pathways need further development to clarify the adaptive changes that are triggered by disease and to generate new targets for drug development. Animal models will also be useful for testing novel therapeutic approaches for inducing the regeneration of injured, dysfunctioning or dead sensory cells and for guiding their re-integration into the appropriate sensory pathways. Stem cell implants are an example of such a therapy (Li *et al.*, 2004).

There is an increasing need for clinical testing of new compounds and for innovative therapies for sensory disturbances based on new knowledge about cell survival/regeneration in specific sensory cells (Cowey *et al.*, 1989). These therapies include genetic and stem cell approaches, as well as pharmacotherapy, the replacement of deficient enzymes and bio-engineering. There is now an unparalleled opportunity for translational research, and reports of reliable genetic associations will help to refine treatment choice. For example, there is huge potential for the treatment of hearing loss, and drugs are already available that ameliorate the predictable, damaging effects of excessive noise and ototoxic drugs. The greatest challenge in the context of hearing is to develop drugs for the regeneration of sensory cells following noise-induced and age-related hearing loss. Similar approaches could be applied to the other senses. As regards retinal diseases, phenotype/genotype correlations in patients and mouse mutants will contribute to our understanding of the underlying pathophysiology. Genetic investigation of large families with AMD could help to identify candidate genes and modulator genes involved in genetic mutations that affect vision and/or hearing, as has already been proposed for the gene that encodes the sodium bicarbonate cotransporter NBC3 (Bok *et al.*, 2003). Similarly, research on retinal neurons will lead to the development of neuroprotective measures that could help prevent visual impairment. Electronic prostheses for the blind have shown promise (Chader *et al.*, 2009) and this line of research should be pursued by European researchers if they are to remain dominant in the field.

### Significance of increased research

Research on sensory disturbances has suffered from limited funding because of the erroneous assumption that it is adequately funded under neuroscience research programmes. This trend has only been partially reversed in recent years. Vertical integration of basic science, genetics and clinical research is increasingly possible, but further investment at each of these levels is necessary. We need increased clinical trial capacity, which means reversing the long-term trend towards fewer clinical trials in Europe. It is now vital to conduct clinical research into the genetic, developmental and/or nutritional deficits and early life experiences that influence vulnerability to sensory abnormality and disease. Turning biological small science into large-scale research programmes will require a pan-European approach, in order to pool the existing expertise and ensure that large numbers of patients with these relatively rare diseases are recruited to clinical trials.

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## Theme VI. 4: From bladder, sexual and other vegetative disturbances to function and basic aspects of the autonomous nervous system

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### Background

The autonomic nervous system, through its sympathetic and parasympathetic components, innervates every organ in the body. It therefore has the potential to cause problems involving target organs (resulting in bladder, sexual and bowel dysfunction) and key integrative systems (such as control of body temperature and blood pressure, through innervation of sweat glands, blood vessels and heart). Both genders and all age groups are affected, though the elderly are particularly prone to autonomic disorders. Bladder and sexual dysfunction may significantly alter the prognosis of a particular neurological disorder and represent a major negative influence on the patient's quality of life, often overshadowing the sensory-motor deficits, which are the neurologist's central concern. Bladder dysfunction affects 96% of multiple sclerosis patients 10 years after diagnosis, for example, and sexual dysfunction is highly prevalent in neurological patients. Importantly, neurogenic bladder and sexual dysfunction may be amenable to treatment after

appropriate assessment. Orthostatic hypotension is increasingly recognised in neurological and medical disorders, such as diabetes mellitus. Fifty percent or more of cases of syncope (fainting) are due to autonomic causes. Autonomic disorders are therefore likely to account for a considerable amount of morbidity and mortality, which is under-recognised.

### Past achievements in Europe

European researchers have led the field of autonomic disorders that affect patients with neurological diseases and overlapping medical disorders (such as neuropathy in diabetes mellitus). Many of these advances are described in clinical textbooks (Mathias & Bannister, 2002; Vodusek, 2008). Particular examples include advances in understanding bladder and sexual dysfunction, multiple system atrophy, orthostatic hypotension and syncope. Guidelines for investigation and treatment of autonomic disorders, established by European researchers, are used worldwide (Lahrman *et al.*, 2006).

### Proposal

Major gaps exist in our knowledge of the epidemiology of autonomic disorders. Little research has been carried out on the pathology, pathophysiology and aetiology of these disorders either. Even normal brain control of basic functions such as micturition and blood pressure during wakefulness and sleep (Cortelli & Lombardi, 2010) is not yet fully understood. Research on the pathophysiology of neurogenic autonomic dysfunctions from the molecular level to the systems level will advance the possibilities of prevention and treatment, an urgent unmet need in the context of many neurodegenerative diseases, including Parkinson's disease (Zesiewicz *et al.*, 2010). There is considerable basic research, either in the field of autonomic disorders or in overlapping fields, such as cardiovascular research, that should be readily translatable into the treatment of these patients, but has not yet been translated. Practical management of patients varies widely across Europe. Good clinical practice guidelines need to be established and promoted. Diagnostic testing needs to be standardised. Both health workers and the general population should be educated about the importance of discovering, evaluating and treating autonomic dysfunction. A Europe-wide research programme should bring researchers together in focal and multidisciplinary studies of bladder and sexual function, blood pressure control (especially orthostatic hypotension) and syncope. The genetic basis of neurally mediated syncope – particularly its most common form, vasovagal syncope – needs to be mapped.

### Significance of increased research

Such a research programme will help to reduce morbidity and even mortality due to autonomic disorders, for example by reducing the trauma that results from orthostatic hypotension and neurally mediated syncope. There is a 30% misdiagnosis rate in epilepsy and the majority of those misdiagnosed cases probably have an autonomic cause (involving neurally mediated syncope). These misdiagnosed autonomic disorders have a major impact on the working lives, driving performance and treatment response of affected individuals. Treating bladder and sexual dysfunction will considerably improve the quality of life of those affected. Treating the former will reduce renal failure and associated problems, for example in patients with spinal cord injuries. Interventions that correct the primary deficit in many types of autonomic dysfunction already exist, so better identification of these conditions could lead to significant reductions in the burden of autonomic disorders. Research



will also generate novel drug therapies, producing potential benefits for millions of patients.

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## CONSENSUS DOCUMENT ON EUROPEAN BRAIN RESEARCH

# Chapter VII: Towards a better diagnostic and therapeutic approach: enabling technologies

Section editor: Ian Ragan

### Theme VII. 1: Molecular imaging: from man and animals to mechanisms at cellular and biochemical levels

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#### Background

Molecular imaging is an emerging field in which the tools of molecular and cell biology are being combined with state-of-the-art technology for noninvasive imaging. The technology of molecular brain imaging involves an entirely new way of studying biological processes in the brain, as well as diagnosing, monitoring and managing brain diseases. It is based on existing imaging technology such as positron emission tomography, single photon emission computed tomography, magnetic resonance imaging (MRI) with advanced contrast agents, magnetic resonance spectroscopy and optical imaging. Each of these imaging modalities has certain advantages and disadvantages, which means that the combination and integration of information provided by each of them yields new information.

#### Past achievements in Europe

Molecular imaging has already assisted significantly in the assessment of basic pathophysiological processes and in providing earlier and more precise diagnoses (Brooks, 2005). The correlation of molecular genetics with molecular and morphological brain imaging of tumours (Walker *et al.*, 2004), Parkinson's disease (Aime *et al.*, 2000) and depression has already yielded significant insights into basic pathophysiological processes and in the case of depression, into the effects of treatment (David *et al.*, 2005). However, while molecular imaging centres are well established in the USA, similar centres are not yet widespread in Europe. Many pharmaceutical companies now consider molecular imaging a key element in drug development and validation, so centres which have been set up specifically for the purpose of conducting research into novel methodologies and applications of molecular imaging to brain pathophysiology are needed in Europe. The European Commission has supported molecular brain imaging research in the past, for example through the Fifth Framework Programme Concerted Action, Neuroreceptor Imaging in Mild Cognitive Impairment, and a Network of Excellence called Diagnostic Molecular Imaging. Although important for establishing networks in education, training and scientific collaboration, these networks do not allow for long-term strategic investment in molecular imaging research. Europe is the home of many excellent research centres but the new field of molecular imaging is expanding rapidly, and it needs that long-term investment if Europe is to become a leader in the field.

#### Proposal

The first goal is the optimisation of technology for the integration of radiotracer, MRI and optical imaging methods. This requires the coregistration of molecular information acquired by each of these imaging modalities on a voxel-by-voxel basis. The second goal is to speed up the development of so-called smart imaging probes that are specific for a given molecular process, and which can be detected and localised by at least one imaging modality. However, there is currently no formal network that allows for the transfer of new probes from the pharmaceutical industry to academia, and so no systematic way of realising this potential. Another major aim is to develop the noninvasive characterisation or phenotyping of animal models.

Molecular imaging will play an increasingly important role in clinical neuroscience in years to come. It will add to the understanding of pathophysiology in human brain disease by combining phenotyping and genotyping. It will aid the early diagnosis of major brain diseases and enable the monitoring of disease progression, including the effects of drug therapy. Research into the correlation between gene expression as assessed by molecular imaging, and physiological processes in diseased areas of the brain, will become possible. The correlation of specific gene expression patterns with physiological counterimages will in turn allow the calculation of drug delivery parameters to specific, molecularly defined disease processes in a spatially confined fashion. Finally, molecular imaging is now increasingly used as a surrogate marker to determine and quantify brain disease progression, including the effects of drug therapy (Knudsen *et al.*, 2004). Together with genetic investigations, molecular brain imaging is the most promising tool we have to pave the way for the development and assessment of new treatment strategies for brain diseases. Not only does the noninvasiveness of the methods open up unprecedented opportunities for studying and characterising the healthy brain, it also allows for longitudinal assessments to establish changes in molecular patterns during the initiation, progression and treatment of brain disease.

#### Significance of increased research

Intensifying research in molecular imaging will lead to new possibilities for: noninvasive characterisation or phenotyping of patients for early diagnosis of neurodegenerative disease; imaging disease progression and assessing the effects of molecularly targeted therapies; and imaging the dynamics within neural networks after gene and stem cell-based therapies, for example following ischaemic stroke.

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## Theme VII. 2: Neuro-imaging: from clinical application to basic principles

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**N. Ramsey** – Psychiatrist

### Background

Our growing understanding of the genetics, physiology and biochemistry of brain diseases is driving an ever-quickening rate of therapeutic discovery and clinical testing. To test therapeutic effectiveness, in experimental animals as well as in humans, it is essential to measure the longitudinal response to a new therapy. Some brain diseases, such as Parkinson's disease, Alzheimer's disease (AD) and schizophrenia, begin long before they are clinically symptomatic (DeKosky & Marek, 2003). Thus, ideal longitudinal markers should signal the presymptomatic stage, when therapies could be applied that would stem or reverse the process of neuronal loss or other tissue damage that gives rise to symptoms. For many brain disorders, neuro-imaging (including electrophysiological brain monitoring) meets the requirements of such a biomarker.

### Past achievements in Europe

Most of the tools we use to image and monitor the nervous system were created in Europe. From Röntgen (Nobel Prize 1901), who used X-rays to visualise the skull, to Peter Mansfield, who applied nuclear magnetic resonance to imaging (Nobel Prize 2003), Europeans have led the field. In the past decade, the Trans-European Network for Positron Emission Tomography has laid the foundations of a solid and productive group of collaborative researchers in the basic and clinical neurosciences. In functional imaging studies, statistical parametric mapping, born in London, is now used as a standard throughout the world (Friston *et al.*, 1995). Many other analytic techniques, including voxel-based morphometry and dynamic causal modelling, were also created in London. Three of the four leading manufacturers of neuro-imaging equipment have their headquarters in Europe.

### Proposal

#### Development of more effective neuro-imaging tools

Higher field magnetic resonance imaging (MRI), at upwards of 7 tesla, may permit the earlier diagnosis of brain diseases such as AD by showing the loss of neurons from layer II of the entorhinal cortex

(Augustinack *et al.*, 2005), or of brain tumours by revealing a small cortical neoplasm after a first seizure. It may also improve the quality of MR spectroscopy and thereby permit the chemical diagnosis of a number of genetic disorders. Research on ways to improve the utilisation of 1.5 and 3T MRI is also needed, including techniques like parallel acquisition and more advanced coil technology. The development of new biological contrast media for MRI, that could be used in humans, would allow for the study of metabolic and pharmacologic aspects of brain function with the high anatomical resolution and versatility that this technique provides. We need to continue to develop the diagnostic and therapeutic applications of selective stimulation and recording with peripheral or central electrodes, including deep brain stimulation and transcranial magnetic stimulation. These techniques are important, not only for basic research on systems neurobiology, but also in presurgical evaluation, to minimise surgical trauma, and in the study and treatment of pain, basal ganglia disorders and, potentially, several psychiatric disorders.

#### *Understanding the origins of the signals detected with imaging techniques*

Functional imaging techniques detect metabolic and vascular responses that are coupled to neuronal activity. This complex relationship should continue to be the subject of research, as it will provide vital information for interpreting imaging signals in health and in disease (Logothetis, 2008).

#### *Imaging as a marker of polygenic disorders*

Polygenic brain disorders may manifest imaging and clinical changes of such complexity that they defy easy classification and so hinder research into the genetic changes that are responsible for them. What we now call schizophrenia, for example, could be the result of a variety of genetic disorders. Uncovering the hidden relationship between clinical, imaging and other findings in patients ('endophenotypes') and their genetic make-up may help clarify the genetic underpinning of such diseases.

#### *Determination of the rate of progression of disorders of the nervous system; evaluation of brain plasticity*

Often the rate of disease progression is measured more reliably with neuro-imaging than with other biological markers, allowing clinical trials based on imaging biomarkers to be completed more quickly and with fewer patients. How the brain is re-organised after trauma, stroke or other injuries should be clarified and that knowledge used to devise better rehabilitation techniques.

#### *Significance of increased research*

Along with genetics, neuro-imaging will change the way medicine is practised, allowing for prevention, earlier diagnosis and more effective treatment of some of the most prevalent brain disorders, including AD, depression, schizophrenia, epilepsy and stroke. It also carries the promise of individualised medicine, with targeted therapies and fewer adverse effects.

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### Theme VII. 3: Identification of blood-based biomarkers to aid diagnosis of psychiatric disorders

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#### Background

The emerging technology of proteomics has potential for use in biomarker discovery for diseases including psychiatric disorders. Currently, there are three basic methods used in proteomic analysis: two-dimensional difference gel electrophoresis (2D-DIGE); liquid chromatography-mass spectrometry (LC-MS); and multiple analyte profiling immunoassay panels. There are several companies which specialise in the latter approach, including the US-based Millipore Corporation and Rules Based Medicine, Inc, and UK-based Pronostics Ltd. The main technical challenges concern the inability of existing methods to resolve more than a small fraction of the estimated proteome, the difficulties associated with validation and, perhaps most importantly, the translation of validated biomarkers to a platform suitable for routine use in laboratory or clinical settings. In this regard, the multiple analyte profiling platforms are the method of choice.

#### Past achievements in Europe

There have been several successful European research programmes, which have applied proteomic techniques to psychiatric disorders. A good example of the 2D-DIGE approach was provided recently by a group in Ireland which identified cytoskeletal abnormalities in post-mortem brain tissue taken from psychiatric patients (English *et al.*, 2009). Our group in the UK used a state-of-the-art LC-MS system to identify several biomarkers in serum of first-onset schizophrenia patients, and many of our findings were validated using immunoassay techniques (Levin *et al.*, 2009). So far, no studies based on the multiple analyte profiling approach have been published in the case of psychiatric disorders, although the technology has been applied in clinical studies of nonpsychiatric diseases.

Clinical psychiatrists are becoming increasingly receptive to the idea of using empirical means such as biomarker assays to improve their ability to accurately diagnose psychiatric disorders. In addition, pharmaceutical companies routinely use biomarkers to facilitate drug development and validation in the context of nonpsychiatric disorders. An example is the measurement of human epidermal growth factor receptor 2 (HER-2/neu) gene expression for guiding treatment and monitoring disease progression in patients with breast cancer (Radpour *et al.*, 2009).

The hype, which surrounded early reports of the promise of proteomics, has not yet been justified. This is because new technologies are required to make the analysis of greater proportions of the proteome possible, and because further development is needed in the

validation and translation phases. Since the new field of biomarker discovery is expanding rapidly, Europe needs to invest in it over the long term if it wishes to lead the field.

#### Proposal

A diagnostic panel for a psychiatric disorder such as schizophrenia should make use of a readily accessible biosample such as blood, saliva or urine. For the initial discovery phase, this will necessitate the use of multiple technologies, including new methods that make it possible to study protein function. Such methods will increasingly be needed for the identification of distinct subproteomes, protein complexes, post-translational modifications and rare, low-abundance molecules.

The first goal should be the identification of a preliminary panel of biomarkers using a well-characterised clinical cohort. It is important that samples be taken from first-onset, antipsychotic-naïve patients who have been matched for baseline characteristics to a control population, to minimise any effects of confounding factors. This is critical because most schizophrenia studies have investigated chronic, antipsychotic-treated patients. The reason for the scarcity of studies of first-onset patients is that they are difficult to recruit. Even large, specialised centres can only recruit around 20–30 such patients a year, and few centres follow strict standard operating procedures for the collection of biosamples. Therefore, it will be important to identify cooperative clinical centres in order to obtain the highest possible quality of results.

The second stage of the process will require the translation of any identified candidate markers to a high-throughput platform, such as the multiple analyte profiling immunoassay panels, for validation using additional clinical cohorts. The third stage will be to determine if the biomarker panel is capable of identifying patients either before or during the earliest phases of disease onset, and the final stage will be to ensure that the panel is specific for the disease as opposed to related disorders.

#### Significance of increased research

Proteomic technologies will play an increasingly important role in clinical psychiatry in years to come. They will add to our understanding of the pathophysiology of psychiatric diseases by combining phenotypes with molecular fingerprints, aid the early diagnosis of such diseases, and make it possible to monitor both disease progression and the effects of drug therapy. In addition, the fact that they allow the correlation of specific biomarker fingerprints with more molecularly defined disorders and with physiological changes such as drug treatment effects, means that they open up the possibility of personalised medicine.

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## Theme VII. 4: Drug delivery to the brain: from human use and clinical experiments to cellular mechanisms

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### Background

Brain tumours, neurodegenerative disease, stroke and head trauma lead to death or severe disability in a large number of patients in Europe. Knowledge of molecular mechanisms and possible therapeutic targets for these conditions is steadily increasing, but effective means of delivering a therapeutic molecule to its target are often lacking. The intact blood-brain barrier (BBB) with its specialised microarchitecture, and the physiology of the cerebral vascular system itself, severely restrict the transport of molecules from the blood into the brain tissue. So finding new and better systems for delivering drugs to the brain would make cellular targets accessible that for the moment, remain beyond our reach.

### Past achievements in Europe

There have been many successful European research programmes that have refined techniques for delivering drugs to the brain. For example, implantation of biodegradable wafers impregnated with cytostatic drugs has already entered clinical use for local delivery of those drugs (Westphal *et al.*, 2003). For compounds that do not penetrate the BBB, including fusion proteins, the principle of convection-enhanced delivery (CED) has been implemented and improved. In CED, the flow of fluid between cells (intercellular bulk flow) is exploited to transport molecules towards the target. Using catheters that are precisely inserted into the brain, one can direct this flow within the brain tissue by adjusting volume and infusion rate (Bidros *et al.*, 2010). Cells that have been genetically engineered to secrete bioactive molecules have been encapsulated into inert matrices, which can be placed safely into the brain instead of directly implanting the cells. Another technology that circumvents the BBB is nanotechnology (liposomes, nanoparticles), which is designed to target specific areas of brain tissue via binding sites linked to the carrier surface that interact specifically with the targeted tissue. Researchers have been working intensively to develop 'intelligent liposomes' that are directed towards cerebral endothelial cells (Blasi *et al.*, 2009). Drugs that bind specifically to molecules that are expressed in gliomas have entered clinical trials, and novel molecular imaging techniques make it possible to visualise these targets in patients (Schnell *et al.*, 2009). Europeans have been at the leading edge of this research, which, if it became more of a collaborative effort, would proceed much faster.

### Proposal

To circumvent the BBB or to directly target the brain capillary endothelial cells (BCEC), we need to understand in detail the cellular characteristics of the brain's microvascular architecture. The biology of BCEC turns out to be very different from that of other microvascular endothelial cells in the body. Research in vascular cell biology has to be intensified to improve our knowledge of the microenvironment of the cerebral capillaries in health as in disease. Since BCEC seem to differ in the two states, disease-specific vascular biology has to be investigated urgently. Once we have identified the cellular transport mechanisms of BCEC in a given disease state, we may be able to exploit those mechanisms for transvascular transport of

drugs within an affected region. As the study of vascular physiology (including permeability and perfusion studies) *in vivo* is critical to this endeavour, suitable animal models must be developed that mimic the conditions in which therapy will be delivered.

For those molecules that cannot cross the BBB, more research is needed into the physiology of bulk flow within the brain in different disease conditions, since bulk flow can be exploited using CED for delivering large molecules. We are beginning to understand bulk flow in the vicinity of tumours with a perifocal oedema, but this understanding now has to be extrapolated to other diseases (such as focal ischaemia and neurodegenerative disease). With the help of imaging techniques such as diffusion tensor magnetic resonance imaging, simulations can now be developed for visualising and monitoring the distribution of the drug solvent. Computerised modelling of CED must be developed to enable precise, pretreatment planning of drug distribution. 'True' molecular imaging (ligand-specific positron emission tomography, for example) can be used to visualise targets and to monitor the target-specific distribution of drugs. Carrier optimisation involves the construction of carrier systems such as nanoparticles whose surface is specifically linked to ligands expressed on the surface of the target cells. Those target cells may be the affected cells themselves, or cells in the microvascular system that supplies the affected tissue. If we consider using antibodies as 'anchors' of therapeutic agents such as fusion proteins or radionuclides, the size of the antibody or fragment thereof will be crucial. *In vivo* experiments are needed to design antibody fragments that have a high selectivity and specificity, and that permeate the designated tissue following direct intrasional application. In general, we need to exploit new methods for the noninvasive, specific application of active molecules (Pasha & Gupta, 2010).

### Significance of increased research

Better drug delivery could significantly improve the treatment of diseases that are otherwise fatal or severely disabling, by making drug therapy more targeted. As well as reducing the suffering of patients, this would have a tremendous impact in terms of reducing both the individual and the societal costs of these diseases. Moreover, many of the new technologies developed or refined during the research projects outlined here would generate industrial investment with economic benefits for Europe. Only multinational projects that link the most innovative and productive groups in basic and clinical research with those working in industry can assure Europe a leading role in this fast-growing field.

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## Theme VII. 5: Neurogenesis, neuromodulation and neurostimulation of the brain

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### Background

The aim of neuromodulation is to normalise dysfunctions of the nervous system and other organ systems by interfering with the electrical, chemical and pharmacological properties of the nervous system. Neuromodulation can take various therapeutic forms, including:

1. Chronic electrical stimulation of the brain, spinal cord or any other neural structure by means of an implanted electrode connected to a pulse generator.
2. Direct infusion of pharmacological substances into the cerebrospinal fluid or the brain tissue through a catheter connected to a programmable pump.
3. Implantation of young neural cells, such as stem cells, to replace neurons lost through degeneration.

In this research theme we will focus on neuromodulation by electrical stimulation (ES). ES can be considered for the treatment of neurodegenerative diseases such as Alzheimer's, Parkinson's (PD) and Huntington's diseases, as well as for multiple sclerosis, cerebral, coronary and peripheral ischaemic conditions and hypo- and hyperkinetic movement disorders other than PD. Other central nervous system diseases that are potentially eligible for ES treatment are central and other forms of neuropathic pain (Simpson, 2003), headache, tinnitus, epilepsy and psychiatric disorders including obsessive compulsive disorder and severe major depression (Krames *et al.*, 2009). A prerequisite for ES treatment is that more conventional therapies are not, or are no longer, effective. Though the diseases mentioned here have very different epidemiologies, they are all disabling, chronic and mostly nonfatal, hence they impose a heavy burden on individual patients and their families. Patients have a much reduced quality of life and have many healthcare needs.

### Past achievements in Europe

The field of neuromodulation by ES has grown rapidly over the last two decades. The first disorders to be treated by ES, in the 1980s, were chronic benign neuropathic pain, ischaemic diseases (of the heart and extremities) and movement disorders, but ES of the brain was generally accepted only after the first publication of the dramatic effects of chronic ES of the subthalamic nucleus in patients with PD (Pollak *et al.*, 1993). Other targets were later identified for the treatment of movement disorders, and more recently for the treatment of psychiatric disorders, epilepsy and tinnitus (Krames *et al.*, 2009; Bartels *et al.*, 2007). In 1991 the International Neuromodulation Society (INS) was founded by a group of European medical specialists from different disciplines. The INS has since grown into a worldwide, multidisciplinary organisation (International Neuromodulation Society, 2010).

### Proposal

Many clinical and research centres across Europe are focusing their activities on ES treatment and exploration of new applications for the technique. However, despite the efforts of the INS, close collaboration on both national and international levels is lacking. Many outstanding issues can only be resolved with multinational cooperation in the clinical and experimental domains. Multicentre studies are needed to

standardise indications and operation techniques, and there must be close contact between the participants in order to increase the number of patients enrolled in such studies. The same is true for experimental research, which is currently fragmented between many different, independent laboratories. New knowledge is not rapidly or efficiently exchanged yet. Ongoing clinical research into ES for movement disorders should be extended to randomised clinical studies, which are virtually lacking in this era of evidence-based medicine. Questions remain as to the potential neuroprotective effects of ES, the disorders which can be treated with it and the ideal patient profile, not to mention the optimal target for each disorder, the adverse effects associated with each target, the optimal use of sophisticated perioperative neurophysiological monitoring (micro-electrode recording) and the configuration of the stimulation parameters. ES is currently being applied in a small number of centres, in trials with limited patient numbers, for the treatment of other diseases such as angina pectoris, neuropathic pain and headache. Again, multicentre collaboration both in clinical and in basic research will pave the way to refining these applications and to understanding the underlying mechanisms. Stimulation devices should be refined in terms of miniaturisation, ease of self-programmability and incorporation of closed-loop systems, which provide therapy on demand.

Knowledge of the mode of action of ES remains limited. Basic research should therefore be a priority and integrated into collaborative projects. European funding could help to:

1. Create European implantation databases, similar to those used for cardiac implants.
2. Coordinate activities between European centres for sharing basic research and collaborating in clinical studies.
3. Facilitate the exchange of PhD students and the creation of scholarships.
4. Finance implants in clinical studies for new ES applications.
5. Promote dedicated annual congresses for each application.
6. Facilitate cost-benefit studies.
7. Construct an infrastructure for conveying information to the public in cooperation with patient organisations.

### Significance of increased research

Although ES has shown tremendous therapeutic potential in a variety of pathological conditions, its precise place in the therapeutic armoury remains to be determined. Neurostimulation for some disorders has now gone beyond the experimental stage, and research is therefore needed to establish that therapeutic role and the mechanisms of action of ES, as well as its potential competitive or synergistic interactions with more classical, mainly pharmacological, therapeutic approaches. Numerous clinical studies of ES have demonstrated a high degree of clinical efficacy and patient satisfaction, as measured by improvement in their quality of life. Many patients affected by the kind of disease that is amenable to ES treatment tend to withdraw from society. Once treated, however, some are able to reintegrate into family and social life and even to take up or resume work. Cost-benefit analyses should now be carried out in order to demonstrate the benefits of this rehabilitation for society as a whole.

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## Theme VII. 6: Nanotechnology: from basic science to brain applications

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### Background

Nanotechnology refers to a wide range of technologies that measure, manipulate, or incorporate materials and/or features with at least one dimension between approximately 1 and 100 nm. Such applications exploit the properties, distinct from bulk macroscopic systems, of nanoscale components. More specifically, in the context of biomedicine, nanotechnology can be broadly defined as ‘nanosized structures that possess new or enhanced properties that are unattainable at both smaller (quantum) and larger (macromolecular) levels’. Nanotechnologies and nanostructures offer promise in different fields of medicine, including imaging and drug delivery.

### Past achievements in Europe

The major obstacle to drug delivery to the brain is the blood-brain barrier (BBB), which is characterised by a lack of fenestrations, reduced pinocytotic activity and intracellular tight junctions. Nanoparticles are among the noninvasive techniques that have been proposed to overcome this barrier, since some nanoparticles can cross the BBB, and after they have done so, their nanoscale size means that they can be transported into the cell and into cellular compartments including the nucleus. By conjugating nanoparticles to antibodies or having them bind to immune cells, it is possible to direct their delivery to tumour markers on target tissues, for example, thereby decreasing systemic exposure to them. Superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle magnetic resonance contrast agents are increasingly being used in the central nervous system (CNS) for characterising particle delivery, monitoring trafficking of particles and cells, and visualising intracerebral tumours (Weinstein *et al.*, 2010). Neuronal transport of nanoparticles has been described, involving retrograde and anterograde movement in axons and dendrites as well as perineural translocation. This is important because it means that nanoparticles may be able to access the CNS via sensory nerves in the respiratory tract, which in turn means that nasal drug delivery becomes a possibility (Misty *et al.*, 2009).

### Proposal

A new generation of nanovectors could incorporate multifunctional compounds and allow multistage, complex delivery of therapeutic compounds and augmented cellular therapies. The application of nanotechnology to cell therapy and tissue engineering is promising for brain and spinal cord injury treatment. Stem cells have been shown to selectively target injured brain and spinal cord tissue and improve functional recovery (Kubinová & Syková, 2010). Superparamagnetic iron oxide nanoparticles can be used to label transplanted cells so that they can be detected. Magnetic resonance imaging is then a suitable method for tracking the grafted cells *in vivo*.

A coordinated research effort involving basic and clinical researchers and industry is needed to translate nanotechnology into these novel targeted and personalised therapies, and the aims of this effort should be as follows:

1. To develop biologically compatible nanofibre scaffolds that mimic the structure of the extracellular matrix and serve as a permissive bridge for axonal regeneration, or as a drug delivery system.
2. To acquire data in humans regarding the long-term clearance of these agents from the brain.
3. To study the pharmacokinetics and pharmacodynamics of drugs with nanocarriers in order to determine the effective dosing and duration of therapy. It will also be important to investigate the transport rate of differently sized nanoparticles to the brain, and to evaluate how surface modifications and the introduction of specific ligands affect that rate.
4. To develop complementary agents to improve nanoparticle localisation, characterisation and follow-up in diverse neurological lesions. This will be necessary for improving the detection and diagnosis of CNS tumours, for example, and for tracking tumour progression and response to classic chemotherapies [particularly anti-angiogenic drugs (Benny & Pakneshan, 2009)]. Another potential application will be the enhanced delivery to the CNS of anti-HIV drugs (Rao *et al.*, 2009).

### Significance of increased research

Nanovectors, nanostructures, nanoplatfoms and nanoscale complexes could facilitate less invasive and more selective treatments of brain tumours and other CNS pathologies. The use of nanotechnology in medicine, and more specifically in targeted drug delivery, is set to spread rapidly, with obvious benefits for both patients and society.

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## Theme VII. 7: Brain mechanisms and applications of brain-machine interfaces

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### Background

Brain-machine interfaces (BMI) use a person’s brain activity to operate external devices such as switches, computers or prostheses. Their clinical application includes direct brain communication in completely paralysed patients and restoration of motor function in patients with high spinal cord lesions or chronic stroke. For the totally

paralysed, BMIs are essential for communication, particularly for completely locked-in patients suffering from amyotrophic lateral sclerosis (ALS), Guillain-Barré syndrome or subcortical stroke. In Europe, more than 1% of the population suffers from chronic stroke, and more than 10 million people are wheelchair-bound or permanently incapacitated after spinal cord lesions, including many young people. Rehabilitation and treatment of these conditions currently have low success rates.

#### *Past achievements in Europe*

Europe plays a leading role in BMI research, particularly for noninvasive BMIs for paralysed or locked-in patients (Birbaumer *et al.*, 1999; Pfurtscheller *et al.*, 2005), while the US still dominates the invasive implantation of electrode grids in monkeys and basic invasive BMI research (Nicolelis *et al.*, 2004). One US lab has received permission to implant 100 commercially developed microelectrodes in the motor cortex of five quadriplegic patients with the aim of restoring motor function and control, and the first patient has already been implanted. European labs have for the first time established and successfully tested noninvasive BMIs for locked-in patients with ALS. The website BCI2000 (BCI2000), set up jointly by European and US researchers, allows access to programming guidelines for BMIs free of charge. However, large-scale clinical testing of invasive and noninvasive BMIs is lacking both in the US and in Europe. Only a concerted, Europe-wide research effort can ensure Europe's continuing contribution to the BMI field.

#### *Proposal*

The theoretical and experimental separation of invasive and noninvasive human BMI research is not useful for the field or for future applications. The aim of the European effort should be to develop and test both invasive and noninvasive, commercially available and affordable BMIs that are tailored to specific applications. BMIs for direct brain communication and for motor restoration should have priority.

Several methodological problems have to be solved before the proposed large-scale clinical studies can proceed. For noninvasive BMIs, electrode grids for long-term scalp recordings are needed, along with amplifiers with direct current properties that lie close to the electrodes. In the invasive case, we need small electrode grids for subdural implantation in the human cortex, with a minimum of 100 electrodes spanning about 1 cm<sup>2</sup>, that remain stable over years. If possible, transmission of brain activity to external devices should occur wirelessly, to allow movement and to minimise the risk of infection from cables leaving the head or body. A longitudinal European study following patients with ALS is needed to establish the efficacy and economic viability of a noninvasive BMI for communication. This device should allow measurement and control of oscillatory brain activity and evoked brain responses, including slow brain potentials, for the control of external spelling devices, internet browsers and other 'inclusion' technologies. The feedback modality for the patient has to be auditory or haptic because of defective vision in the locked-in state. A subgroup of patients who agree to subdural implantation of electrodes will provide comparison with those opting for the noninvasive approach. The control offered by the BMI should also be compared with that of devices that exploit changes in autonomic functions such as skin conductance to drive communication aids.

Under the auspices of two large European studies, chronic stroke patients with well-defined brain lesions who are not responsive to any conventional treatment, and a group of high spinal cord injury patients, should be trained to move their prosthetic devices or muscles

directly via brain activity recorded through invasive or noninvasive electrode grids. Magnetoencephalography (MEG)- and electroencephalography (EEG)-BMIs for motor applications should be compared, because MEG may allow more degrees of freedom for movement control. In stroke patients, for example, local control of hand areas in the lesioned brain may be acquired more easily with MEG during initial training phases, with later transfer to EEG then becoming much easier. Rehabilitation outcome and follow-up measures should include motor performance improvement in everyday life, but also cortical reorganisation induced by the BMI training as measured by functional magnetic resonance imaging or positron emission tomography.

#### *Significance of increased research*

After completion of the proposed research, the European consortium will offer specific BMI devices on a commercial (insurance-covered) basis, along with standardised training procedures for the different types of paralysis. This will help to reduce the enormous costs of rehabilitation for patients with all types of paralysis and handicap, as well as the costs of installing facilities with disabled access in public places. The availability of such devices will also bring relief to patients, their families and the communities in which they live. The current discussion concerning euthanasia, physician-assisted suicide and quality of life will profit from a solid scientific knowledge of the locked-in state. The proposed European research effort will also bear fruit in terms of new applications for BMIs – for example, in early seizure detection and seizure control in intractable epilepsy.

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### **Theme VII. 8: From neural networks, oscillations and coding to neuro-informatics**

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#### *Background*

To understand how the brain performs its many and complex integrated functions, and to use that knowledge for the treatment of disease, we need to analyse it from the molecular to the behavioural and cognitive levels and integrate that knowledge. This is a major challenge for neuroscience, because only in a few systems has it been possible to link the cellular and the behavioural levels to date.

Due to the high number of dynamically interacting components in the brain, it is generally impossible to gain fundamental insights into a brain function through experiment alone, and modelling is in most cases a necessary complementary methodology (Markram, 2006; International Neuroinformatics Coordinating Facility). During the last few years, new types of supercomputer have made it possible to create



simulations of networks of millions of neurons, based on detailed experimental knowledge about the properties of each cell type and their ion channels, receptors and associated neurotransmitters (Markram, 2006; Djurfeldt *et al.*, 2008). This has opened up novel ways of testing integrated brain function that were not possible previously. The entire cortex of the mouse brain can now be simulated at a high level of detail, for example.

Neuro-informatics is composed of three major components: computational neuroscience (modelling), development of a federation of databases and development of information technology (IT) tools for analysis. Rapid advances in IT have enabled us to build databases that span the molecular, behavioural and clinical levels of analysis, through all levels in between. Databases of this kind greatly facilitate the transfer of information from the clinical domain to that of structural biology, for example, and vice versa. Another important area of neuro-informatics is IT-based collection of clinical data relating to brain disease, which opens up the possibility of discovering new and unexpected correlations through data mining. Neuro-informatics will no doubt become as important for neuroscience, as bio-informatics has been for cell and molecular biology.

#### *Past achievements in Europe*

Recent developments in the computational analysis of networks and microcircuits of the neocortex, hippocampus and motor system have provided important new insights (Markram, 2006; International Neuroinformatics Coordinating Facility). Europeans have contributed significantly to the bridging of cellular and network levels and remain at the forefront of this field, promoting major new research efforts including those of the Gatsby Charitable Foundation and the Wellcome Trust at University College London in the UK. The large-scale simulations planned by the Blue Brain project at the Ecole Polytechnique Fédérale de Lausanne in Switzerland have attracted global interest (Markram, 2006), as has the large-scale modelling taking place at Sweden's KTH Royal Institute of Technology (Djurfeldt *et al.*, 2008).

European researchers have also taken a very active part in the development of neuro-informatics. In 2005, European, American and Japanese researchers created the International Neuroinformatics Coordinating Facility (INCF) (International Neuroinformatics Coordinating Facility), which was first proposed by the Global Science Forum of the Organisation for Economic Co-operation and Development (OECD). The research ministers of the participating OECD countries have recommended that neuro-informatics should be allocated more resources. The INCF, which is financed by its 15 member states and has its secretariat in Stockholm, has initiated several large research programmes, including one on multiscale modelling.

#### *Proposal*

To understand the operation of the nervous system at the network level and ultimately in a global context, we need to understand the intrinsic function of the brain's different functional modules. This means investigating the operation of cortical columns, microregions in the basal ganglia such as striosomes and matrisomes, the microzones of

the cerebellum and the neuronal networks that coordinate motor behaviour, among other functional modules. Research designed to elucidate the dynamic interplay of neural subsystems will afford new insights into the mechanisms underlying motor disorders such as Parkinson's disease. This will require a dedicated effort to identify, for each microcircuit, which neurons are active, how they interact synaptically, which transmitters and receptor subtypes they use, and the palette of ion channels that are expressed in each type of neuron, giving it its particular membrane properties. This work will in turn rely on a wide variety of methodologies, from transgenic and molecular techniques to cellular physiology and pharmacology, behavioural methodology and modelling. The latter will encompass biochemical modelling at the single cell level, biophysical realistic network modelling and exploratory models at a more abstract level. For each microcircuit, the collaboration of several researchers with complementary expertise will be required to achieve these goals. To aid them in their efforts, a range of complex and interoperable databases must be designed. We envisage a situation in which specialists from many different disciplines, both basic and clinical, all contribute to that design process. The resulting databases may eventually contain a large variety of complex information, such as the dynamic representation of activity levels in different brain areas during behaviour, along with the electrical activity at the single cell or ion channel level and the relevant clinical and molecular data.

#### *Significance of increased research*

No fundamental understanding of brain function can be gained from studying it only at the cellular and molecular levels. We must also understand it at the network and systems level. Until now, a correlation between a gene, neurotransmitter or receptor subtype and a change in brain function or clinical condition has been no more than that, a correlation. Knowledge at the intervening levels is required if we are to understand the neural basis of that function or dysfunction. It will be important, therefore, to focus on the microcircuit, because this serves as the interface between the molecular/cellular level and the systems/behavioural level. The proposed multilevel or multiscale approach will rely on a combination of complementary experimental and modelling techniques. This work will in turn be facilitated by the development of neuro-informatics databases. Such an approach will generate new understanding of the healthy, physiological function of different brain systems, as well as the many devastating brain diseases and the modes of action of various pharmacological therapies.

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