

SUPPLEMENT

Consensus document on European brain research

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1.0 Executive summary

Brain disease psychiatric and neurologic disease combined represents a considerable social and economic burden in Europe. Data collected by the World Health Organization (WHO) suggest that brain diseases are responsible for 35% of Europe's total disease burden. An analysis of all health economic studies of brain diseases in Europe, published by the European Brain Council (EBC) in June 2005, estimated the total cost of brain disease in Europe in 2004 to be €386 billion. That burden is set to grow, mainly due to the fact that the European population is ageing.

Investment in brain sciences does not match that burden now, let alone in the future. Brain research received only 8% of the life science budget in the European Commission's Fifth Framework Programme, which represents less than 0.01% of the annual cost of brain disorders for that period. Over the last decade, Europe has been losing ground to the USA and Japan in terms of both basic and clinical research. Many of Europe's young researchers are taking up posts in the USA and staying there. Big pharmaceutical companies are fleeing Europe for the USA, taking their drug development programmes with them.

Research in the brain sciences now holds the promise of therapies that halt and even reverse neurodegeneration, of better diagnostic tools, neural prostheses for the paralysed and drugs for depression and anxiety that are tailored to the individual, thereby eliminating or reducing side effects. Our growing understanding of the normal brain could lead to better prevention of brain disease and to more effective teaching methods. The need for innovative treatments has never been greater, and Europe boasts clusters of excellent researchers in biotechnology who could collaborate with brain scientists and the pharmaceutical industry to realise this promise.

But if Europe is to seize these opportunities and meet the challenge of brain disease, it needs to go forward on the basis of greater collaboration between countries, greater collaboration between industry, academia and patient organisations, and increased investment in the brain sciences. The EBC was formed in 2002 to bring together scientists, clinicians, the pharmaceutical industry, charities and patient organisations from all over Europe to campaign for these goals. It takes a novel, bottom-up approach to research policy, and in developing this consensus document,

it aims to promote a greater and more focused effort in this area, to improve public understanding of the brain sciences and above all, to support brain research as a priority under the European Commission's Seventh Framework Programme (FP7, 2007–2013).

The research programme outlined here was first conceived by the EBC board. An outline was sent to all member organisations and a number of individual experts for comments. Following that, a table of contents was developed. The 45 research themes were written by groups of experts from across Europe who represent a wide range of disciplines. Each one contains a proposal for future research on a specific brain-related theme which the EBC believes could form the basis of one or more integrated projects or strategic targeted research projects (STREP) funded under FP7. The EBC has deliberately focused on the major diseases and then described the basic research needed to understand and treat or perhaps even cure those diseases. The programme is therefore constructed "from man to molecule" and not the other way round, with equal importance attached to basic and clinical research.

The EBC suggests that each of the proposed integrated projects or STREP should be awarded a budget in the order of €10 to 15 million. In addition, brain research should be treated as an important element of many other parts of FP7, such as the European Research Council and research programmes on information technology and the causes of violence. Any research programme that concerns human behaviour should, by definition, take account of brain research. The EBC envisages that the priority for brain research it proposes at the European level will translate into higher priority for brain research at the national level, and this document may also serve as a starting point for the development of national consensus programmes. It seems likely that consensus conferences on brain research in Europe may further develop the themes and ideas discussed here. An EBC task force may also be established to further the consensus process.

In general, increasing funding in the brain sciences would bring enormous economic returns by lightening the burden on healthcare systems and increasing the productivity of affected individuals—and might easily pay for itself. The human and social returns of such an investment are inestimable. And the time to act is now.

2.0 BRAIN DISEASES

Background

Brain research is all research—both basic and clinical—pertaining to the central and peripheral nervous systems and their diseases. Brain diseases are all those disorders which affect the central and peripheral nervous systems, including half of all traumatic injury and half of all congenital abnormalities that cause disability. The EBC has adopted these definitions in an attempt to unify the various disciplines whose interest is the brain, the spinal cord and the peripheral nerves. For several reasons, particularly the promotion of research and teaching as well as for public information campaigns, it is extremely important that all those with an interest in brain research and brain diseases work together and not as separate specialities. From a clinical point of view, the EBC has no intention of changing the existing structure of specialities and even supports sub-specialisation, recognising that as the management of brain disorders becomes more complicated, increasing specialisation is necessary. However, for research, teaching and public education purposes the grouping of diseases under different specialities is artificial and potentially counter-productive. For example, dementia is not a neurological disease, a geriatric disease, a psychiatric disease or a general disease, but all four. Patients with dementia are diagnosed and cared for by psychiatrists, neurologists, geriatricians and general practitioners. They benefit from the breadth of expertise represented by all these clinical specialities, and basic scientists investigating the causes of dementia also benefit from taking a multidisciplinary approach to the problem.

The human brain is extremely complex. When that complexity is disturbed, the resulting diseases are debilitating because basic functions such as movement, communication, interaction and interpersonal feelings can be affected. Normal brain function is the condition for our daily functioning and the ability to adapt to a changing environment—for example, the advent of the high speed information society. The study of normal brain function and of brain diseases are therefore equally important.

Over the last few decades brain research has advanced dramatically. Progress has been made at all levels, from understanding genetic mechanisms and the function of individual neurons, to cell-to-cell communication and the ability to image the intact, awake human brain non-invasively—both in adults and during development. Disease processes such as

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Abbreviations: ADHD, attention deficit hyperactivity disorder; ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; ASP, autism spectrum disorders; BBB, blood brain barrier; BCEC, brain capillary endothelial cells; BSE, bovine spongiform encephalopathy; CED, convection-enhanced delivery; CDBE, Cost of Disorders of the Brain in Europe; CJD, Creutzfeldt-Jakob disease; COSBID, the Cooperative Study on Brain Injury Depolarisations; CVD, cerebrovascular diseases; DBS, deep brain stimulation; DMD, Duchenne's muscular dystrophy; EADC, European Alzheimer's Disease Consortium; EAE, experimental autoimmune encephalomyelitis; EBC, European Brain Council; EBCI, European Brain Injury Consortium; EEG, electroencephalography; EFNA, European Federation of Neurological Associations; EFNS, European Federation of Neurological Societies; ENU, ethylnitrosourea; GBD, Global Burden of Disease; INCF, International Neuroinformatics Coordinating Facility; INS, International Neuromodulation Society; LTP, long term potentiation; MEG, magnetoencephalography; MRI, magnetic resonance imaging; OCD, obsessive compulsive disorder; OECD, Organisation for Economic Cooperation and Development; PET, positron emission tomography; PTSD, post traumatic stress disorder; PVS, persistent vegetative state; RABRE, Resource Allocation for Brain Research in Europe; SCI, spinal cord injury; SERRS, surface enhanced resonant raman spectroscopy; SPECT, single photon emission computed tomography; SSRI, selective serotonin re-uptake inhibitor; SUDEP, sudden unexpected death; TCR, T cell receptor; TMS, transcranial magnetic stimulation; TSE, transmissible spongiform encephalopathies; UPS, ubiquitin-proteasome system; WHO, World Health Organization; YBOCS, Yale-Brown Obsessive compulsive Scale

degeneration and traumatic, ischaemic and inflammatory brain damage, as well as the brain's own repair mechanisms, are now much better understood. Huge progress has been made in the epidemiology and classification of brain diseases, and in their social consequences.

These advances are in part due to the breaking down of barriers between disciplines such as anatomy, physiology and biochemistry, all of which share an interest in the brain. Experts from these disciplines now work together in the institutes of neuroscience that have been created by many universities. Clinicians and basic scientists have realised the advantages of collaborating and exchanging information. Basic research that has led to the elucidation of disease mechanisms has often been inspired by observations in patients, and many basic scientists now work closely with clinicians to ensure translation of their research to the clinic.

The EBC encourages this increasingly multidisciplinary approach by ensuring that the collaboration includes industry and patient groups. This consensus document is the natural extension of that philosophy, in that it proposes that the European Commission invests more in a multidisciplinary, multinational approach to brain research.

Burden of brain diseases

Brain diseases are a major public health problem in Europe and beyond. In its study, Global Burden of Disease (GBD) 2000,¹ the WHO presented global epidemiological data in terms of years lost due to premature death (YLL) and years lost to disability (YLD), where YLD was calculated by multiplying the years lived with a disability by a disability factor. The overall measure of loss of health developed by the WHO, called disability adjusted life years (DALY), is the sum of YLL and YLD. By extracting the relevant data from the GBD 2000 study, the EBC calculated that in Europe, brain diseases account for 23% of YLL, 50% of YLD and 35% of all DALY.² In other words, brain diseases account for 35% of the burden of all diseases in Europe. That impressive figure reflects the debilitating nature of brain diseases and the fact that people usually live with them for many years.

An analysis of all epidemiological and health economic studies in Europe published by the EBC in 2005, called Cost of Disorders of the Brain in Europe (CDBE), measured the impact of brain diseases differently.³ It took a holistic view of costs:

- healthcare costs (hospital care, ambulatory care, drugs)
- private and public costs outside the medical sector (including nursing home costs and services or goods for private homes)
- indirect costs (including limits on work capability, absenteeism and early retirement).

The analysis found that across 28 European countries (the European Union plus Iceland, Norway and Switzerland) with a total population of 466 million, 127 million people or 27% are affected by at least one brain disease. The total cost of brain diseases amounts to €386 billion, or €829 per European inhabitant—the equivalent of more than 25 Channel Tunnels.

What follows is a brief description of the 12 most costly brain diseases, listed alphabetically, with their total prevalence in Europe and annual cost for the year 2004, as calculated by the CDBE study.

Addiction

Addiction is a pattern of symptoms including compulsion to use a substance; impaired capacity to control that use; tolerance of, withdrawal from and preoccupation with the substance and continuing use despite harmful consequences [6.2, Theme 3].

Prevalence: 9 million people (alcohol and illicit drug addiction only)

Annual cost: €57 billion

Affective disorders

Affective or mood disorders comprise a group of disorders characterised by clinically significant mood disturbances. Three major categories are recognised: major depression, bipolar disorder, and cyclothymic and dysthymic disorders. The CDBE study focused on major depression and bipolar disorder [6.2, Theme 1].

Prevalence: 21 million people
Annual cost: €106 billion

Anxiety disorders

The spectrum of anxiety disorders ranges from panic disorder and generalised anxiety disorders to various types of phobic disorders, and includes obsessive-compulsive disorder and post-traumatic stress disorder (PTSD) [6.2, Theme 2].

Prevalence: 41 million people (excluding PTSD)
Annual cost: €41 billion

Brain tumours

Brain tumours are classified into primary and secondary, where the former originate in the brain itself and the latter are metastases originating in another part of the body. Secondary brain tumours are always malignant, while primary brain tumours occur both in benign and malignant forms [6.3, Theme 9].

Prevalence: 135,000 people
Annual cost: €4.6 billion

Dementia

According to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised (DSM-III-R), the criteria for dementia include demonstrable evidence of impairment in memory and either (a) impairment in one other intellectual function (abstract thinking, judgement or impairment of higher cortical functions) or (b) personality change [6.3, Theme 1].

Prevalence: 5 million people
Annual cost: €55 billion

Epilepsy

Epilepsy is a chronic condition characterised by repeated unprovoked seizures, where an unprovoked seizure is one that occurs in the absence of precipitating factors. Disease severity varies considerably from patient to patient, with the severe cases mainly accounting for the high costs [6.3, Theme 4].

Prevalence: 3 million people
Annual cost: €15.5 billion

Migraine

Migraine is a severe form of headache occurring in attacks that usually last between four hours and three days, with disabling accompanying phenomena such as nausea or vomiting, severe intolerance to light, sound, odours and body movement [6.4, Theme 1].

Prevalence: 41 million people
Annual cost: €27 billion

Multiple sclerosis

Multiple sclerosis is an acquired inflammatory and neurodegenerative disorder of the central nervous system (CNS), mediated by the immune system, whose symptoms include visual and sensory disturbances, limb weakness and gait problems. Despite its limited prevalence, it has a large social and economic impact due to its chronic and debilitating nature [6.3, Theme 5].

Prevalence: 380,000 people
Annual cost: €9 billion

Parkinson's disease

Parkinson's disease is one of the most common chronic neurodegenerative diseases. Main symptoms are bradykinesia or slow movement, rigidity, rest tremor and postural instability.

Non-motor symptoms include depression, psychosis and gastrointestinal dysfunction [6.3, Theme 2].

Prevalence: 1.2 million people
Annual cost: €11 billion

Psychotic disorders (schizophrenia)

Schizophrenia is the most chronic and disabling of the psychotic disorders. It is characterised by disorganised thinking, and sometimes delusions and auditory hallucinations. Though not a highly prevalent disease, it is among the most costly [6.2, Theme 4].

Prevalence: 3.7 million people
Annual cost: €35 billion

Stroke

Stroke is a vascular disorder characterised by the sudden death of brain cells due to a reduced or blocked supply of blood. The symptoms depend on the site of the stroke, but can include both motor, speech and memory deficits [6.3, Theme 3].

Prevalence: 1 million people
Annual cost: €22 billion

Trauma

Traumatic brain injury is an insult to the brain that leads to temporary or permanent impairments of cognitive abilities and physical functioning. Head injury, sustained for example during a road traffic accident or fall, contributes significantly to the outcome in half of all deaths resulting from trauma [6.3, Theme 7].

Prevalence: 700,000
Annual cost: €3 billion

The treatment revolution

Until a few decades ago, a patient with Alzheimer's disease, stroke or traumatic brain injury faced a bleak future with a diminished quality of life, reduced productivity in terms of their capacity to work and contribute to family life, and dependence on carers. Without a cure or any means of alleviating the patient's symptoms, for example by prescribing drugs that slowed the progression of a degenerative disease or neuro-rehabilitation to restore some of the brain function lost through stroke or traumatic brain injury, the doctor's role was reduced to advising the patient on coping strategies. Over recent decades, however, the treatment of brain diseases has undergone a revolution. Here are a few examples:

The drug levodopa (L-dopa) effectively treats the symptoms of Parkinson's disease in many patients, though the disease remains incurable. Now, however, patients for whom L-dopa is not effective, or no longer effective, may be considered for deep brain stimulation (DBS), a surgical technique developed for the treatment of movement disorders in Grenoble, France in the late 1980s. DBS has proved effective for the treatment of tremor, bradykinesia and gait problems in Parkinson's disease [6.3, Theme 2], and now in refractive major depression and other mood disorders. Moreover, basic research in DBS for brain diseases is revealing novel therapeutic targets which could in future be modified non-surgically, for example with drugs.

The WHO's GBD 2000 study judged that a patient with a severe migraine attack was as disabled as one with active psychosis, dementia or tetraplegia. But thanks in part to the European discovery of messenger molecules that play a pivotal role in migraine such as serotonin, also called 5-hydroxytryptamine (5-HT), new therapeutic agents called 5-HT₁ B/D agonists (triptans) have been developed [6.4, Theme 1]. These drugs do not prevent migraine attacks, but they do relieve the symptoms very effectively in many patients, allowing them to lead more normal and productive lives.

Depression and anxiety are now commonly treated with the class of drugs called selective serotonin re-uptake inhibitors

(SSRIs). These are no more effective than the older anti-depressant drugs, but they have fewer side effects. Growing understanding of the brain circuits involved in appetite control and in addiction are leading to the development of pharmacological treatments for substance use disorders [6.2, Theme 3], eating disorders and obesity [6.2, Theme 6].

Research in traumatic brain injury has shown that the primary traumatic insult sets in train a cascade of events in the brain which leads to secondary injury, and that this secondary injury can be exacerbated by systemic insults such as hypoxia. That knowledge has led to the development of therapeutic strategies which limit the extent of secondary damage [6.3, Theme 7]. It is also now accepted practice in Europe to initiate rehabilitation procedures immediately for traumatic brain injury patients, as this has been shown to enhance their recovery. Patients who are left paralysed or locked in, due to traumatic brain injury, motor neuron disease or some other cause, are now able to communicate and to exercise control over their environment—for example, operating switches—through brain machine interfaces that have been developed and continue to be refined in Europe and the USA [6.7, Theme 7].

Burden of disease set to grow

The population of Europe is ageing, with more people—especially women—living longer than 80 years. This trend, along with declining birth rates, is producing profound demographic changes in Europe and a corresponding shift in its disease profile. The first Global Burden of Disease study⁴, published in 1996–97 by the WHO, World Bank and Harvard School of Public Health, predicted marked increases in the burden of non-communicable diseases, and of brain diseases in particular, to the year 2020. The authors of that study predicted that in 2020, major depression would rank second among the 10 leading causes of DALY after ischaemic heart disease. Over the next 20 years, the number of people suffering from brain diseases could grow by as much as 20%. The arrival of the information age, with its emphasis on information transmitted through the visual channel in large quantities and at high speed, will inevitably have an impact on a brain that underwent most of its evolution in a very different environment. To what extent that impact will translate into brain diseases is difficult to determine, but social changes such as the increasingly wide geographical dispersal of families, the weakening of extended family networks and the changing role of women mean that fewer relatives stay at home to care for patients with brain diseases. The burden and cost of that care is therefore shifting onto professional care services.

The resource shortfall

Brain diseases are the most burdensome and costly group of diseases to society, as established by the WHO data and the CDBE study. However, they only account for 15% of direct health care costs in Europe. This discrepancy may be partly due to the fact that there are fewer treatments or cures for these disorders than for other types of diseases, but it is also due to a shortfall in healthcare provision, which in turn reflects inadequate training of clinicians in brain-related subjects as well as a shortage of material resources. For example, stroke is currently the second leading cause of mortality in Europe after ischaemic heart disease. Yet despite the proven value of specialised stroke units in the management of acute stroke, most stroke patients are still admitted to general medical wards. Major depression, the third most burdensome disease in Europe, often goes undiagnosed or untreated. Dementia, which ranks fourth, accounts for the majority of nursing home residents, yet most of those people have never been diagnosed.

It is often stated that drugs for brain diseases are overused and too costly, but drugs for brain diseases account for only 8% of total drug sales, a small figure compared to the proportion of

the total disease burden represented by brain diseases. In fact, sales of drugs for brain diseases represent 3% of the total cost of those diseases. Considering that they keep large numbers of patients out of hospital and in employment, the probability is that they pay for themselves many times over—though prospective health economic studies are needed to prove that statement. What is certain is that for some of the diseases which threaten to become more prevalent as the population ages, a “pharmaceutical gap” is opening up because there are no effective treatments for them, or current treatments are inadequate. Alzheimer’s disease, which is currently incurable, is a prime example. Major depression, for which current treatments are only partially effective, with occasionally severe side effects, is another.

Investment in brain research is insufficient. Brain diseases account for 35% of the burden of all diseases in Europe and are more costly than diabetes and cancer put together. The only way to prevent them becoming more costly still is to intensify research efforts towards improving prevention, treatment and health care. Yet brain research received only 8% of the life science budget in the European Commission’s Fifth Framework Programme (FP5, 1998–2002), €85 million, which represents less than 0.01% of the annual cost of brain diseases for that period. Resource Allocation for Brain Research in Europe (RABRE) is an ongoing project of the EBC, due for completion in June 2006, which looks at current levels of funding for brain research and brain disorders in the EU. Pending the outcome of that survey, the EBC proposes that European funding for brain research should be increased to 0.13% of the annual cost of brain diseases, or €500 million per year.

Against the background of the European Union’s stated goal to increase expenditure on R&D to 3% of the gross domestic product by 2010, the increase in funding for brain research that the EBC is proposing is tiny, even taking into account that brain research funding is greater at the national level than at the European level. There is, however, another way to judge the value of such an increase in investment. In its 2005 CDBE study, the EBC estimated the total cost of brain diseases in Europe to be €386 billion. Due to the scarcity of data in several of the countries included in that study, plus the fact that it restricted itself to the 12 most prevalent brain diseases, that was considered a conservative estimate. The true cost of brain diseases in Europe could be much higher, perhaps in the range of €500 to 700 billion. If the increased research efforts relieved only 0.1% of that burden, they would pay for themselves. With the burden set to grow, can Europe afford *not* to invest in brain research?

Losing the edge in R&D

Historically, the pharmaceutical industry has been one of the strengths of European science and technology, but now the USA and Japan are leading the field. In 2001, the European Commission published a report (known as the Pammolli Report after one of its authors) which found that the European pharmaceutical industry was losing competitive advantage to the USA. According to that report, Europe was “lagging behind in its ability to generate, organise and sustain innovation processes that are increasingly expensive and organisationally complex”. Its analysis suggested that Europe’s competitiveness in this area was inhibited by fragmented markets and research systems. Between 1990 and 2000, R&D spending in the USA was double that spent in Europe. The Pammolli Report also found that eight of the top 10 best selling medicines came from the USA, compared with only one from Europe.

Another survey of the pharmaceutical industry commissioned by the European Commission in 2004 described the implications of the changing costs of R&D for innovation in the EU as “potentially alarming”.⁶

It highlighted two significant threats:

- The lower R&D costs in lower income parts of the world
- A loss of competitiveness to the USA, despite a cost advantage in undertaking trials in Europe.

Europe may be about to lose that cost advantage, however, as India and China become increasingly attractive locations for low cost, large scale clinical trials. Like the Pammolli Report, the 2004 survey also pointed to fragmented research systems in the European Union. In the USA, by contrast, there is better cooperation between public and private research organisations carrying out basic research (including cooperation between universities, research institutions and the pharmaceutical industry). In particular, the US National Institutes of Health (NIH) is seen as coordinating public and private research, and bringing together funds, scientific knowledge and centres of excellence. There is currently no equivalent of the NIH in Europe, though virtual institutes of health have been proposed to fill that role.

Beyond the pharmaceutical industry, basic brain research is also chronically underfunded in Europe. The European Commission's Sixth Framework Programme (2002–2006) allocated €2.2 billion to the life sciences over the four years of the programme, while the annual budget of the NIH is about US\$30 billion (€25.4 billion). Individual EU member states spend much more on research than the EU through the Framework Programmes, nevertheless there is a mismatch between research funding in the USA and Europe, and that mismatch has led to a brain drain of some of the best European researchers to the USA. Eastern European countries, which tend to have invested poorly in research infrastructure and equipment, nevertheless continue to produce many well-trained and highly motivated scientists who seek posts abroad. Those scientists represent a potentially vast resource for Europe—especially as more Eastern European countries join the EU—but with its current funding conditions Europe is failing to attract them.

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3.0 BRAIN RESEARCH

Need for innovative drugs

Closing the pharmaceutical gap for brain diseases will have major economic and social benefits, particularly if the drugs developed are also made available in the developing world. A pharmaceutical gap has been identified for Alzheimer's disease and major depression, two brain disorders which threaten to become more prevalent in the coming decades. Despite major advances in our understanding of the pathophysiology of Alzheimer's disease and the introduction of symptomatic drug treatment more than 10 years ago, the biological basis of the disease is not fully understood and there is no cure. In depression, although chronic stress is a known risk factor, we still do not understand the brain's stress regulating systems well enough to have identified drug targets there. Nor do we understand how treatment with existing antidepressants brings about adaptive changes in those systems or in the brain's neurotransmitter systems in general [6.2, Theme 1].

A survey undertaken for the UK's Department of Trade and Industry (DTI) in 2005¹ looked at the UK pharmaceutical industry's views on the production, use and regulation of psychoactive drugs—that is, drugs for the treatment of what the report referred to as mental health, as well as drugs that enhance cognition or modify mood. The survey found that, in the industry's view, people in the developed world now expect to have effective treatments for mental health disorders—notably depression, anxiety and schizophrenia—and that there is increasing demand for drugs that affect the course of the disease rather than just relieve symptoms. The industry foresaw that the heavily marketed “blockbuster” drug would give way to personalised medicine, and it no longer believed that “magic bullets” exist for complex brain disorders. There is now a consensus in the industry that effective new treatments will require combination therapies, including psychological strategies, and an individualised approach based on screening, early detection and monitoring.

The survey also solicited the views of pharmaceutical and biotechnology companies on the treatments that would become available in the next 20 years for specific brain disorders or symptoms. These are some of their responses.

Addiction

The industry was cautious about the commercial viability of treatments designed specifically to treat addiction, and was concerned about the ethics of preventative treatments for those considered at high risk. Nevertheless, it believed that drugs would be developed that would enhance executive function (eg decision-making), decrease impulsivity and reduce stress and craving, whether aimed at addiction or not, and that these could form part of an addiction treatment regimen that also included psychological therapies for reducing craving and preventing relapse.

Pain

Significant advances in our understanding of central sensitisation mechanisms and the role of inflammatory factors in pain meant that the industry was optimistic that new treatments for neuropathic, inflammatory and functional pain were on the horizon. Some are already in early development. However, there were concerns over safety, abuse potential and the poor predictive value of animal models, among other issues.

Depression, anxiety disorders and schizophrenia

New treatments for depression and anxiety are likely to be available in five to 10 years', and companies are already researching in these areas. The prevention of schizophrenia was not regarded as inconceivable from the scientific point of view, though the industry expected it to prove very difficult and ethically challenging. In the meantime, adjunct therapies will be developed in the near future that support the atypical antipsychotic drugs currently prescribed for schizophrenia, by enhancing their efficacy and reducing side effects.

Sleep disorders, attention deficit hyperactivity disorder (ADHD), mood stabilisation and autism were other areas in which the industry predicted the emergence of novel treatments in the next 20 years. Drugs for cognitive enhancement were seen as more challenging, because of difficulties with predictive animal models and clinical trials, not to mention ethical issues.

R&D: much more than drugs

R&D is not just about innovative drugs, it is also about better diagnostic tools. For example, European research groups are pioneering the development of cerebrospinal fluid and neuroimaging biomarkers for early identification of Alzheimer's disease. These are still experimental, but as soon as clinicians are able to diagnose the disease in its preclinical phase, based on these or other markers, they will have a broader window of

opportunity in which to treat it [6.3, Theme 1]. Given that the prevalence of Alzheimer's disease doubles with each successive five year age band after the age of 65, delaying the onset of the disease by five years will reduce the total number of patients by 50%. Even in the absence of a definitive cure, such a postponement—which in turn depends on earlier diagnosis—will have a substantial impact on the burden of Alzheimer's disease. Likewise, in Parkinson's disease, patients lose up to 70% of their nigrostriatal neurons before they show symptoms. Clearly the brain contains a lot of spare capacity, and if the disease could be identified and treated before the critical number of neurons are lost, the prognosis for the patient would improve and the burden of the disease reduced [6.3, Theme 2].

Schizophrenia has a genetic component. Several candidate genes for the disease have already been identified, and their contributions to its pathophysiology are being studied in animal models. Those studies will help to clarify the interaction between genetic and environmental control of developmental mechanisms in the formation of neural circuits. Neuroimaging will help to reveal if patients with schizophrenia show abnormalities in those same circuits. Since schizophrenia is a developmental disorder, the possibility of identifying people who carry mutated versions of the relevant genes—perhaps by a simple blood test—or who start to show changes in the relevant neural circuits early in life, as revealed by neuroimaging, could mean that doctors will be able to treat or prevent the disease by intervening at an age when neural circuits are still particularly plastic and capable of recovery [6.2, Theme 4].

Such improvements in diagnosis rely, in part, on the development of better imaging techniques. In the neuroimaging domain, higher field magnetic resonance imaging (MRI) than is currently available for clinical purposes (5–9 Tesla) could permit the earlier diagnosis of brain diseases such as Alzheimer's disease by showing the loss of neurons of layer II of the entorhinal cortex, or of brain tumours by revealing a small cortical neoplasm after a first seizure [6.7, Theme 2]. It may also improve the quality of magnetic resonance spectroscopy and so make possible the chemical diagnosis of a number of genetic disorders. Functional imaging techniques detect metabolic and vascular responses that are coupled to neuronal activity. This complex relation is not yet understood, though it is the subject of intense investigation. When it is understood, it will provide crucial information for interpreting imaging signals in health and disease. To that end, electrophysiological and other imaging techniques are being combined in exciting ways to image the brain at different levels of detail simultaneously—supported by the application of non-linear system mathematics and simulations.

Molecular imaging potentially allows the monitoring of disease progression at the molecular level, including the effects of drug therapy. But molecular imaging techniques need to be improved, for example through 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 method, whether it be radiotracer, optical or MRI [6.7, Theme 1].

The DTI 2005 survey found that, in the opinion of the UK pharmaceutical industry, new diagnostic descriptions, definitions and subdivisions of brain diseases would be developed within a decade, based on a better understanding of the pathophysiology and genetic basis of the disease, but also on patients' responsiveness to treatments. These new definitions will in turn lead to a new generation of drugs with a five to 10 year time lag. A lack of progress in this area could, the industry felt, really hamper the proper understanding and use of genomic information in disease treatment.

But R&D is also about developing new technologies for delivering drugs and other treatments. The mass of new “-omics” data being generated may reveal many potential

new drug targets in the brain, but if the therapeutic molecules cannot cross the blood-brain barrier (BBB), those targets become less attractive to drug designers. By understanding the specialised micro-architecture of the BBB, the physiology of the cerebrovascular system itself and how these restrict the transport of molecules from the blood into the brain tissue, researchers are beginning to find ways to overcome that obstacle [6.7, Theme 4]. Meanwhile, nanotechnology is producing structures the size of large molecules which can be used as vehicles for therapeutic molecules, or in conjunction with polymers, integrated with tissues in micro-engineering applications [6.7, Theme 6]. Progress in this area will be driven by advances in materials science and nanoscale physics, as well as a greater understanding of cell membrane conductance and signalling properties.

Stem cell transplantation is a promising area of research for the repair of brains damaged by neurodegenerative, affective or cerebrovascular diseases [6.2, Theme 6]. One strategy being explored is that of cultivating the required cell type from stem cells *in vitro*, then grafting the differentiated cells into the damaged brain. But the transplantation technique needs to be refined. The anatomical and functional integration of grafts into pre-existing circuits is not yet good enough, and better molecular imaging methods are needed to monitor how the graft functions *in vivo*.

Brain-machine interfaces allow paralysed or locked-in patients to communicate or operate switches or external devices by their own brain signals (for example, electroencephalography (EEG) signals). These are detected either by recording from the patient's scalp or from electrodes surgically implanted in the brain. At the moment, several methodological problems are holding up large scale clinical trials of brain-machine interfaces. In the invasive case, for example, small electrode grids need to be developed which can be implanted subdurally in the cortex and remain stable for years [6.7, Theme 7]. Ideally, the transmission of brain activity to external devices should also occur wirelessly, to allow movement and to minimise the risk of infection from cables leaving the head.

Brain research: a multidisciplinary effort

European Commission surveys have described European biomedical research as fragmented, both between countries and between disciplines. A constant refrain through the research themes of this document, which have been written by leading European experts in brain research in collaboration with representatives of patient organisations and the pharmaceutical industry, is the need for better communication and collaboration between clinicians and basic scientists, between research centres in different countries working in the same area, and between academia, industry and patient groups.

For many of the major brain diseases, researchers have yet to identify the underlying molecular mechanisms, and hence to find cures, because they lack large, well characterised patient cohorts who are followed up over the long term. Such patient populations are crucial for systematic, large scale, prospective studies. They could be rendered more accessible if research centres standardised their procedures for recruiting patients, and for recording clinical and biological data, and then pooled that data in databases according to agreed sampling and storage protocols. The databases could then be contributed to, and accessed by, all research partners. To achieve that goal, the skills of bioinformaticians and experts in data analysis and database architecture will be required, as well as those of clinicians and basic scientists.

Bioinformatics—or more specifically, neuroinformatics—is also a critical component of the current effort to understand the brain at a network level—that is, to understand it at all levels of analysis from the molecular to the behavioural and cognitive, and to integrate the knowledge acquired at each level [6.7,

Theme 8]. This will draw on a wide variety of methodologies, from transgenic and molecular techniques to cellular physiology and pharmacology, behavioural methodology and mathematical modelling. Modellers will be charged with the daunting task of bringing all the different strands of information together into functioning models—informative simulations of the cell, local neuronal networks and even the whole brain—and to build the databases needed to gather that information, as well as the tools to analyse it.

Physicists and engineers could usefully bring their understanding of non-biological systems to the question of how the brain functions at the network level. But their expertise will also contribute more directly to progress in the molecular imaging and neuroimaging fields. For example, advances in these areas could link up with nanotechnology in the ongoing drive to develop highly informative molecular biosensors. These are nanostructures encapsulating reporter molecules that can be detected by non-invasive imaging techniques such as MRI or positron emission tomography. Materials scientists provide the materials out of which the nanostructures are constructed and are also ultimately responsible for the biodegradable wafers, impregnated with therapeutic drugs, which are now being used to deliver those drugs directly into the brain. Convection-enhanced delivery—a concept that has been borrowed directly from fluid mechanics—has also been implemented and approved for the transfer of compounds across the BBB.

Understanding the normal brain

It should be clear from the preceding sections that to understand what goes wrong, it is crucial to understand the normal brain first. The complexity of the brain is such that if we do not understand its integrated functions in health, we cannot hope to disentangle the extra layer of complexity added by disease, or to design therapies to correct it.

In the area of memory, for example, European researchers are responsible for having made the distinction between short and long term memory, and for having defined the concept of working memory. It is now known that different types of memory are associated with differential patterns of activation in the frontal and medial temporal lobes of the brain, and mechanisms potentially involved in the laying down of memories, such as long term potentiation, have been described in detail [6.1, Theme 4]. This basic research opens up the possibility of treating selective memory disorders by increasing the compensatory use of intact memory systems, or by designing novel drugs that selectively target the molecular mechanisms underlying different types of memory. It could also lead to improvements in the diagnosis of memory disorders in affected individuals, and to the development of memory enhancing drugs in healthy individuals.

There is continuing controversy over whether schizophrenia is one disease or several. Most researchers agree, however, that the damage in the schizophrenic brain is sustained early in life, and affects the development of the brain's neural circuits. In vivo brain imaging studies and studies of brains post mortem have pointed to an impairment of cortical connectivity, which may result from the exaggerated loss and/or abnormal selection of connections in the late phases of cortical development. That means that research into the schizophrenic brain and research into normal brain development are likely to cross-fertilise each other, and through that exchange to provide clues to the fundamental basis of cognition and perception [6.2, Theme 4].

Studying the normal brain is important if we are to understand how it adapts to a changing environment, and particularly how it copes in the present high speed information age. Such research could allow us to predict maladaptive changes that might occur in the brain when it is exposed to a certain environment, and hence to prevent them.

But research on normal brain function is not just a necessary starting point for treating disease. We need to understand it in order to be able to interact effectively with one another, to understand how others reach decisions, and to reduce or enhance those variations in human behaviour that, while not considered disease or abnormality, are nevertheless regarded by society as maladaptive or beneficial respectively. Where manipulating a behaviour is either not possible or not desirable, it may still be necessary to understand it in order that society should learn to tolerate it. So, for example, we need to understand why people's sleep needs vary, why teenagers experience mood swings, and how a person's sexuality is determined.

Benefits for society

Some brain diseases have a greater impact on society than others. Only a fraction of the population is criminally violent, for example, but violence is a low frequency, high impact behaviour. It affects the very fabric of society by limiting the freedom of action of many. Researchers now recognise that the propensity of some individuals to act violently is partly due to interactions between genetic predispositions and social stressors at certain critical periods of development, which mould their neural circuits. There is therefore the potential for identifying brain targets for therapy, and treating violent behaviour as one would any other brain disease [6.2, Theme 9]. The medicalisation of violence and aggression is ethically problematic, but clearly the ability to reduce the level of violence in society would have an enormous impact in terms of lifting the constraints on those who currently live with it.

A better understanding of the normal brain could lead to the design of environments (eg toys, television) that are more cognitively stimulating for children. It could also influence teaching methods by indicating how the brain receives and retains information best, and therefore how information could most effectively be delivered. Research has revealed, for example, that there are critical periods for the acquisition of a second language. Since phonemes are recognised and stored by the brain in infancy, children who learn a second language very young are more likely to learn it quickly and to speak the language later in life without an accent.

Advances in nanotechnology in the context of brain research could lead to more intelligent computers and cognitive enhancement via neural prostheses. The Bionanotechnology Interdisciplinary Research Centre at the University of Oxford, for example, was conceived as a "centre without walls" that brings chemists, material scientists, physicists and biologists together to define nanotechnology approaches that can either interact with, or be informed by, biological systems behaviour [6.7, Theme 6]. Researchers there and elsewhere are working on improving interfaces between nanodevices and biological systems, and on understanding the brain's own information processing systems. This could give rise to the linking of powerful computational devices such as quantum computers directly to the human brain. Although this remains a "horizon technology", whose realisation depends on long term investment, it opens up the possibility of "brain-building" via neural prostheses, and of computer driven devices that can learn and take autonomous decisions.

A role for industry

The European pharmaceutical (or bioscience) industry can remain competitive in the world market, or become competitive again, only through increased research effort. Despite the loss of the competitive edge to the USA, Europe still has great resources, particularly in brain research, and it possesses first class biotechnology clusters which could form partnerships with the pharmaceutical industry to exploit novel ideas. Besides the search for innovative drugs, four technological areas should be targeted:

- New techniques for delivering molecules to the CNS and monitoring the fate of those drugs non-invasively over time
- Diagnostic tools for brain diseases and for monitoring disease progression and recovery
- Nanotechnology
- Intelligent computers and brain-machine interfaces.

The traditional blockbuster drug, which is prescribed by primary care physicians and supported by large sales and marketing teams, is likely to give way to a more personal, patient-centred approach in which early diagnosis and prevention play a much greater part than they do today. The drug development process will need to evolve to reflect the fact that symptomatic relief will no longer be acceptable and that more complex, combination therapies will be required that affect the course of the disease and provide a wide spectrum of support for the patient. The design of clinical trials and regulatory procedures does not yet reflect these changes, but the door has been opened to more radical ideas by the new European pharmaceutical directive and the roadmap of the European Agency for the Evaluation of Medicinal Products (EMA). The EC's 2004 survey of the pharmaceutical industry made several recommendations to aid this transition, including encouraging more cooperation between the public and private sectors in Europe, as there is in the USA, and improving communication between the industry and the regulating authorities.

Better communication would, according to the report, ensure that companies were more aware of the requirements of regulators, and regulators of problems identified by the industry. One example would be an agreement between the two on using advances in applied sciences as appropriate end-points for a product in development; another example, a better mutual understanding of the advantages and disadvantages of focusing a product's development on a narrow area where it can be shown to be superior, resulting in a quicker review process than if it were focused on a wide range of therapies.

These and other innovations would speed up the journey of a new drug to market and reduce failure along the way, thus bringing down R&D costs and stimulating more innovation in Europe. One initiative with these goals is already at the advanced planning stage. The Innovative Medicines for Europe Technology Platform (InnoMed), which is supported by the European Commission, the European Federation of Pharmaceutical Industries and Associations and the EBC, aims to define R&D bottlenecks and to identify pre-competitive areas of research and technology development to address these problems. The intention is to create a public-private partnership within the European Commission's Seventh Framework Programme (FP7) that will tackle the major impediments to drug discovery in four important areas: brain research, cancer, inflammatory disease and diabetes. It aims to achieve this through a programme of basic research and the creation of centres of excellence in technology development, as well as in the training of scientists. The project is unusual in placing the patient at the centre of a partnership that will be influential in discussions with the regulatory bodies over the design of clinical trials and risk benefit assessment. Ultimately, InnoMed hopes to foster a multinational, multidisciplinary approach to R&D, and as such it represents a model of the kind of public-private partnership that the EBC would like to encourage.

In the DTI 2005 survey, the companies that were questioned agreed unanimously that there was a need for greater transparency. According to the report, the pharmaceutical industry would play a major part in providing information about how drugs will be used in the next few years, and would "make efforts to restore its tarnished image through early and open publication of clinical trial data". In return, it hoped that its efforts would be reciprocated by increasing understanding from the public and greater appreciation of risk and benefit from the

regulators. This will depend on the building of effective partnerships whose success will in turn depend on trust and openness between stakeholders.

A role for patients

There is a lack of public understanding about the function of the normal brain, the burden that brain diseases impose on society and the vastly improved possibilities for diagnosing, preventing and treating these diseases that have arisen in the last decades. Public education is crucial, because most of us will suffer from a brain disease at some point in our lives, and some of those diseases are preventable. Much has been done to prevent cardiovascular disease and cancers in terms of public education, but comparatively little to prevent brain diseases. For example, it is less well known that smoking increases the risk of stroke, or that smoking during pregnancy increases the risk of brain damage in the fetus, than that smoking is a risk factor for cancer and cardiovascular disease.

In the USA, the 1990s were declared the Decade of the Brain, but similar attempts to create a European Decade of the Brain shortly after that failed. Some national public education campaigns have been successful, and each year the European Dana Alliance for the Brain, along with like-minded organisations, coordinates the highly successful, international Brain Awareness Week—now in its seventh year. Patient advocacy groups have worked hard to educate the public about brain diseases, but their campaigns tend to focus on single diseases, and they compete with each other for public attention. What is needed now is more collaboration between these groups, and between public health authorities at the national level, to coordinate information campaigns about all brain diseases and about the healthy brain, across Europe. People need to know that brain diseases do not just affect the elderly and that "mental" disorders originate in the same piece of neural circuitry as "neurological" or "motor" disorders. They need to know what it is like to live with a disability, and what their own lifetime risk is of developing a brain disease.

Patient advocacy groups also have an important role to play in mediating the patient-doctor relationship; in listening to patients, helping them to express their needs clearly and encouraging them to work in partnership with the doctors who care for them. Doctors typically see the disease; patients see the impact it has on their lives. They are deeply affected by phenomena that cannot be measured by simple clinical tests, such as loss of self-esteem or a feeling of alienation due to the stigmatisation of their disease. Patient advocacy groups must also take responsibility for ensuring that patients educate themselves about their disease, that they are ready to participate in their own treatment and that they have realistic expectations about the outcome.

Patient advocacy groups should stop competing for scarce resources when it comes to research, and recognise that many disorders have important features in common. For example, a number of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and prion diseases are associated with the aggregation of misfolded proteins in the brain. What distinguishes these diseases is not yet known, but understanding this basic phenomenon will probably be relevant to the search for therapies for all of them. Patient advocacy groups representing the different diseases in this group should therefore form coalitions to support the relevant research. They should also collaborate over other areas of common interest, such as ethical issues that arise over stem cell or animal research and the need to change the regulatory practices that are currently stifling innovation in R&D.

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4.0 ETHICS

The essence of what it is to be human lies in the human brain. It is therefore no wonder that brain research raises more ethical questions than any other branch of the life sciences. The solutions to these questions are rarely straightforward, but they must be debated. Brain research must benefit humanity, not harm it, so guidelines for the ethical application of knowledge about the brain must develop in parallel with the research itself.

For example, the definition of “normal” brain function is changing as our understanding of the brain deepens. And that has implications both in terms of defining “abnormal” behaviour and treating it—“normalising” it—and in terms of envisaging how normal behaviour could be enhanced.¹ Clearly this area is an ethical minefield, not least because different cultures may have different definitions of “normal”. But equally, as we understand more about the normal brain, brain diseases are becoming more precisely defined and diagnosed. The distinctions between mental or psychiatric disorders and neurological disorders are being lost, and with them the stigmatisation of the former. As these ideas become more widely accepted, patients suffering from diseases that were once stigmatised will have their dignity restored to them. They will feel less isolated, and more able to ask for treatment and support at an early stage of their disease. The burden of those diseases will therefore be reduced, both in human and in economic terms.

The flip side of that wider recognition and understanding of brain diseases is what some see as the over-medicalisation of abnormal behaviour. If a person is criminally violent, should they be held responsible for their actions, tried in a court of law and sent to prison? Or should they be seen as an innocent victim of the neural machinery which, shaped by their genes and early life experiences, has led them inexorably and against their will into a life of crime? This touches on the existence of free will, and it is an area that has traditionally been the domain of philosophers. More and more, however, brain researchers are contributing to the debate, and it is becoming clear that as science provides better diagnostic evaluation, more effective therapies and better predictive power, the way we think about criminal justice will have to change.² Research is revealing patterns of brain activity and even genes that are associated with aggression and violence [6.2, Theme 9], and in future researchers may be able to treat a violent adult and render him a peaceful and productive member of the community, or predict whether a child will grow into a violent adult, and intervene to divert the child from that fate. But is a predisposition to criminal behaviour sufficient grounds for intervening? These are questions for society at large, not for the scientists who are developing the tests and interventions, and the debates must start now so that the ethical framework is in place when those interventions become realities.

Another area where advances in brain research have raised ethical questions (though hardly new ones) is in the definition of death. Most researchers now accept that death is a process, not an event, and that the point at which it is recognised medically and legally must therefore be to some extent arbitrary. Nevertheless, drawing a line between life and death is important, because patients must be allowed to die with dignity and doctors need to know when they may remove a cadaver’s organs for transplantation. Between coma and brain death brain researchers recognise a third state called persistent vegetative state (PVS), and since the last decade a fourth—minimally conscious state [6.2, Theme 8]. These states are difficult to diagnose, and the case of Terry Schiavo, the brain-damaged woman who was at the centre of a right to die case in the USA, before her treatment was finally withdrawn and she died in March 2005, demonstrates the need for a consensus on terminology, for better clinical tests and for more discussion of the legal status of patients in those states. These developments

will in turn depend on basic research that determines when the brain’s degradation becomes irreversible.

Then there is the definition of life. When does a developing embryo become a human being, and is it acceptable to remove stem cells from embryos for the purposes of research or therapy? At the time of writing almost all embryonic stem cells are harvested from early stage human embryos called blastocysts, but the embryo perishes once the cells have been removed and critics argue that this procedure destroys life to save life. The use of embryonic stem cells to repair brain damage in neurodegenerative disease or after TBI is a promising area of research, which could potentially benefit millions of patients, and Europe has a chance to lead the field because of the restrictions that the current US administration has imposed on federal stem cell research—limiting it to embryonic stem cells drawn from 22 lines approved by President Bush in 2001. As with death, however, the definition of life cannot be determined purely by scientific research. People’s thoughts on these issues are shaped by their religious and cultural backgrounds, so society must agree on what is acceptable. The same holds for animal research, and one of the incentives for creating computerised models of living neurons, neuronal networks or even the whole brain is an ethical one: researchers would be able to test the pharmacological effects of potentially therapeutic molecules on these models rather than on animals.

Patients who are unconscious, comatose or in a PVS cannot consent to or refuse treatment, or volunteer to take part in research programmes. As people live longer, and the technology for prolonging life becomes more sophisticated, there are more and more such patients, and their doctors and relatives are frequently left in the unenviable position of having to decide what is best for them. Living wills and advance directives, in which people specify what treatment they want or do not want in such situations, are increasingly popular, but are not yet legally enforced in most European countries. In other situations where the only available therapy is experimental and time is short, for example when a patient is admitted to hospital with TBI, doctors may find themselves torn between the desire to rapidly instigate the experimental therapy and the ethical requirement to follow proxy consent procedures when relatives are often unavailable [6.3, Theme 7].

For patients with dementia the situation is slightly different. The patient association Alzheimer Europe is in favour of promoting the use of advance directives among such patients,³ but recognises the inherent difficulties with it—notably, who decides when the patient is no longer able to behave autonomously or to take decisions about his or her future treatment? The ethical issues associated with treating brain diseases in children are equally thorny, particularly when an affected child is not regarded as being old enough to give his or her informed consent.

Better diagnosis and more powerful prediction—for example, through genetic testing—means that people now have much more information about the diseases they are predisposed to develop and their likely prognosis. Who should have access to that information? In the UK there is a moratorium on the use of genetic test results by insurers until 2011, but in many countries insurance companies are allowed to ask their customers whether they have taken any genetic tests, and to use this information in “statistically relevant” ways. In other words, they are not allowed to use it to discriminate against individuals. A recent survey conducted as part of the pioneering Genetic Discrimination Project in Australia, led by the Centre for Genetics Education in Sydney, has shown that more people feel they have benefited from genetic tests than have lost out. However a small proportion claim to have suffered negative treatment—for example, by being denied appropriate life insurance.

The advent of increasingly sensitive, non-invasive brain imaging techniques such as functional MRI raises the issue of privacy too.⁴ Researchers have described patterns of brain activity that are associated with romantic love, with moral judgement and even with deception. While the possibility of “brain fingerprinting”—the brain imaging equivalent of the lie detector test—is still way off in the future, if it ever becomes possible, police may well be attracted to it as a way of assessing the mendacity of suspects. Employers, too, might wish to use it in place of psychometric testing, to home in on those job applicants who are good decision-makers, or to weed out those with depressive tendencies. The courts might see its potential for detecting bias in prospective jurors, by measuring the brain correlates of any emotional response they might have to certain groups of people. Neuroscience may be close to a descriptive biology of behaviour, but a predictive biology is not yet on the horizon. Should the police, courts and employers therefore be allowed to peer into our brains, to watch our most intimate thoughts in action and to take such weighty decisions on the basis of that information?

Finally, there is the delicate issue of cognitive enhancement.⁵ As researchers learn more about the neural circuitry that underlies normal learning, memory, attention and vigilance, they see the possibility of enhancing those functions, either with drugs or with “brain-building” neuronal chips or prostheses. Aside from the issue of what the long term effects of such cognitive enhancers might be, including the risk of dependence, and considering that many existing drugs that could be considered enhancers when taken by healthy people are already used “off label”, how should the use of such drugs be regulated, if at all? Ritalin, the drug usually prescribed for ADHD, which improves attention and scholastic performance, is a case in point. Should students sitting exams be tested afterwards for off label Ritalin use, just as athletes are tested for performance-enhancing drugs? And if they test positive, should their results be considered null and void? If, on the other hand, these drugs are to be made widely available, how do you ensure that everyone has equal access to them, so that there is a level playing field in the classroom and workplace? How should teaching methods evolve in a society in which the use of such cognitive enhancers is commonplace? In the DTI 2005 survey of the UK pharmaceutical industry’s views on psychoactive drugs, the industry declared itself reluctant to stray into the area of drugs for non-medical use, largely because of these ethical problems. But it noted that the boundary between medical and non-medical was bound to shift in coming years, and that areas where this is likely to happen first were sleep, mood, stress, anxiety, impulsivity and vigilance.

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5.0 AIMS AND METHODOLOGY

In developing this consensus document, the EBC had the following aims:

1. To cover all brain research, including basic research and research relevant to psychiatry, neurology and neurosurgery.
2. To design the document from a European perspective, focusing on research that requires the collaboration of research groups from several European countries and

trying to avoid research programmes that could equally well be conducted in individual European countries.

3. To establish the highest possible degree of consensus by involving all European research organisations with an interest in the brain.
4. To apply, for the first time, a bottom-up approach where a multidisciplinary group of scientists from academia and industry, together with clinicians and patient representatives, formulated each theme.
5. To widely disseminate a preliminary version of the document in order to obtain consensus.
6. To widely disseminate a preliminary version of the document amongst scientists in order to start the necessary networking processes within Europe.
7. To assist the Commission for Research in designing a brain research programme under FP7.

The EBC is well-suited to take these goals forward because of its broad grass roots representation. Officially founded on 22 March 2002 in Brussels, it has a unique structure that brings together a host of European organisations with a specific interest in the brain. The European Federation of Neurological Associations (EFNA) represents Europe-wide organisations for patients with neurological illnesses, such as the European Parkinson’s Disease Association, Alzheimer Europe and the European Dystonia Federation. The Global Alliance for Mental Illness Advocacy Networks (GAMIAN-Europe) represents associations of psychiatric patients. The European Federation of Neurological Societies (EFNS) represents national societies of neurologists throughout Europe, and the European College of Neuropsychopharmacology (ECNP) is a Europe-wide organisation of psychiatrists, pharmacologists and other basic scientists with an interest in neuropsychopharmacology. The European Association of Neurosurgical Societies (EANS) is a federation of national societies of neurosurgeons. The Federation of European Neuroscience Societies (FENS) represents basic neuroscientists. GlaxoSmithKline, Eli Lilly and Medtronic represent industry, until such time as industry establishes a joint European organisation with respect to brain research. Last but not least, the European Dana Alliance for the Brain (EDAB) and the World Health Organization’s regional office for Europe (WHO-Europe) assist the EBC as observers.

In developing this consensus document the EBC profited from its unique organisational structure. Its multidisciplinary board decided on a list of topics and designed the draft table of contents. That document was sent to member organisations for review and finalised after extensive revision. The member organisations then selected participants for each theme who were considered to be of the highest standard in their fields. Each writing group consisted of between two and six people, each of whom came from a different country and a different discipline. These groups all used a highly structured format for the writing of each theme. The proposals for themes were edited by one editor-in-chief, Jes Olesen, and by section editors who were members of the EBC board. Following that, the collected materials were edited by a science writer, Laura Spinney, who also wrote these introductory chapters based on proposals and information provided by the EBC board. Everybody involved in the writing of the themes was encouraged to send their proposal out to peers for comments and approval, and in this way several hundred scientists and patients have been involved in the development of the document.

To our knowledge this is the first major bottom-up approach to research policy in Europe. We consider this document a starting point in an ongoing effort to create better and better brain research programmes in Europe. We have worked quickly to produce it, because we wanted it to be of use to the Commission for Research in respect to FP7 (2007–2013). It seems likely that,

in future, there will be consensus conferences on brain research in Europe that may further develop these themes and ideas. An EBC task force may also be established to further the consensus process. We consider this document to be a remarkable achievement. We are not aware of any other research programme covering one of the biggest fields in health research that has been endorsed by so many of the organisations that will eventually contribute to it.

The EBC wants brain research to be made a priority under FP7, as the Commission has already proposed it should be. The research programme should emphasise translational research and integrate different disciplines. Each of the 45 thematic papers of this document contains a proposal for future research related to a specific brain-related theme which the EBC believes could form the basis of one or more integrated projects funded under FP7. We suggest that each of these 45 themes be awarded a budget in the order of €10 to 15 million. We have deliberately focused on the major diseases and then described the basic research necessary to understand and treat or perhaps even cure that disease. In other words, this research programme is written “from man to molecule” and not the other way around. This does not mean that the EBC favours clinical research over basic research. If research programmes are to be of interest to a wide audience, they must start with a problem that interests people. There is within the EBC a very positive attitude to basic research, and recognition that major new breakthroughs are often generated in research with no immediate application to human health.

Each of the 45 themes outlined here represents a huge research field. The intention is that as few brain scientists as possible should feel left out of this proposed research programme. A smaller number may eventually be involved in FP7 research programmes, however this document could also have a considerable impact at the national level. The EU has worked hard to achieve a degree of coordination between Europe-wide research programmes and national programmes. We envisage that the priority for brain research proposed by the Commission will translate into higher priority for brain research at the national level. This consensus document was written with the aim of addressing not only scientists but also patient organisations, politicians and other decision-makers. It may also serve those groups in their struggle to gain more recognition for brain research and as a starting point for developing national consensus programmes.

One last aspect needs a comment, and that is the involvement of patients or lay people in this project. They were invaluable partners who were often able to raise important issues that had not been taken into account by the scientists. The present consensus document is therefore, to our knowledge, the first example of a successful involvement of lay people in the development of a scientific research programme. The experience was positive and can only be encouraged in the future.

6.0 SUGGESTED RESEARCH THEMES

6.1 Development, plasticity and ageing of the brain in health and disease

Section editor: Monica Di Luca (FENS)

THEME 1: FROM DEVELOPMENTAL DISORDERS, FETAL, PERINATAL AND POSTNATAL INSULTS, TO GENETICS AND BASIC MECHANISMS OF BRAIN DEVELOPMENT
NOT RECEIVED

THEME 2: FROM ADHD, AUTISM AND THEIR ANIMAL MODELS TO SIGNALLING MECHANISMS AND GENETICS

G Baird – neuropaediatrician, J Buitelaar – child psychiatrist, T Sagvolden – basic neuroscientist, M Bogdan – patient (GAMIAN

Europe), P Tréhin – patient (Autism Europe), M Tricklebank – industry (Eli Lilly)

• A. 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.¹ 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.

• B. 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.^{1–3} 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.¹ European researchers have led the validation of animal models of ADHD.⁴ Other European researchers have proposed an animal model of autism, though it has yet to be formally validated.⁵ Research on complex psychiatric disorders involves experts working in more areas of research than are found in any one European country.

• C. Proposal

ASD and ADHD are thought to arise from complex gene-environment interactions, where the latter may include exposure to neurotoxic substances.¹ 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. If environmental pollutants and toxins are causing disease in children, society is responsible. 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. Several candidate genes for ADHD and ASD are involved in synaptogenesis and neuronal alignment and adhesion. 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.¹ 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 sub-cellular as well as cellular and behavioural functions in order to understand these disorders. For both ethical and economic reasons, these studies will in many cases have to be performed on animal models.

- D. 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, if they are able to become productive members of society and to command higher earnings, those individuals will generate more tax revenue. Collaborations between European industry and universities have an excellent chance of translating their work on neuroscience targets into new medicines and improvements in environmental health.

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THEME 3: FROM SPEECH DISTURBANCES TO BASIC MECHANISMS OF LANGUAGE

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- A. 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 co-morbid features of acute conditions such as stroke and head injury, and of degenerative diseases such as Parkinson's and Alzheimer's diseases. 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.

- B. 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.¹ Large-scale studies have identified different

subtypes of speech and language disorders and their co-morbid features. Functional magnetic resonance imaging (fMRI) has provided neuroscientists with a tool for examining the brain's activation patterns that are associated with different aspects of the language network both during auditory processing and during reading. Meanwhile, advances in electrophysiological techniques such as event-related evoked potentials (ERPs), have made possible the tracking of the temporal structure of brain activation associated with language processing in different sensory modalities.² Advances in structural imaging techniques have provided methods for visualising fibre bundles that form part of the language territory in the left hemisphere,³ and have also made possible the application of statistical techniques for examining group differences in grey and white matter density between normal and language-impaired subjects.⁴ The official guidelines and recommendations for cognitive rehabilitation have now been published under the auspices of the European Federation of Neurological Societies.⁵ These developments have not only provided the necessary diagnostic tools for examining the mechanisms of disturbed speech and language, but have paved the way for novel neuroscience-based intervention programmes (eg transcranial magnetic stimulation (TMS) and electropalatography) for the rehabilitation of individuals with speech and language problems.

- C. 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:

(1) 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.

(2) Well-equipped laboratories are needed which use standardised protocols for the different imaging tools (eg 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.

(3) 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.

(4) 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.

- D. 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 4: FROM LEARNING AND MEMORY TO LONG-TERM POTENTIATION, SYNAPTIC STRENGTH AND OTHER BASIC MECHANISMS

M. Macleod – neurologist, R. Morris – basic neuroscientist

• A. 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, 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 cognitive neuroscience to molecular mechanisms. One promising focus is the study of neural mechanisms of synaptic and neural plasticity, and the possibility that certain aspects of neurodegenerative diseases result from specific disorders of synaptic mechanisms.

• B. Past achievements in Europe

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, and European researchers have made major contributions to this. Europeans discovered or developed: the major distinction between short- and long-term memory and the concept and components of working-memory;¹ the differential patterns of activation of the frontal and medial temporal lobes in different types of memory;² the phenomenon of long-term potentiation (LTP);³ the distinct types and roles of excitatory glutamate receptors in plasticity and learning; and certain mutations of genes (*APP*, *tau*) that are now implicated in familial forms of Alzheimer's disease and fronto-temporal dementia.

European scientists have also worked with researchers in North America and Japan to characterise 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. Similarly, European partnerships with neuroscientists elsewhere in the world are helping to identify the cell biological mechanisms of synaptic plasticity (eg LTP), including the mechanisms involved in trafficking amino acid receptor molecules to synaptic membranes, and signal transduction cascades associated with learning.

• C. 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.⁴ Bottom-up approaches include the search for memory-associated genes and molecules that are activated during memory encoding, consolidation or retrieval.⁵ 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. When it comes to memory and learning, however, our understanding is not sufficiently advanced to allow for fruitful cross-talk between them.

A multidisciplinary approach may not be appropriate, therefore. However, there are domains of analysis in which the top-down and bottom-up approaches meet, as in the recording of the activity of large ensembles of neurons in memory-associated brain areas, and the study of the relationship between these patterns of activity and functional magnetic resonance imaging (fMRI) signals. These do provide opportunities for collaborations between European neuroscientists, and already some groups are linking neuroanatomical, physiological and cell biological data to understand the network principles of local circuits and the information-processing algorithms that they perform. Classic intracellular recording techniques might be supplemented by *in vivo* multi-photon imaging of neural activity using voltage-dependent fluorescent markers, allied to systems approaches. Greater interaction between computational and basic neuroscientists would provide a sharp theoretical focus to the endeavour, as would the more effective management of databases and other neuroinformatics tools.

• D. 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 Alzheimer's disease. 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 pre-symptomatic 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 5: FROM NORMAL AGEING TO BASIC MECHANISMS OF LONGEVITY

H. Tanila – basic neuroscientist, G. Wilcock – neurologist

• A. 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.¹ Age is the most important determinant of an individual’s healthcare needs, so the well-being 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 health care 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.

• B. 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 was made by a European research group.² 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 Europe has made an important contribution at the level of translating basic research into clinical practice. For example, European research was crucial to the development of the cholinergic hypothesis, which drove the design of some existing drugs for Alzheimer’s disease, while one of the first phase II clinical trials of an amyloid-modifying drug for Alzheimer’s disease (R-flurbiprofen), if not the first to be completed, was partly undertaken in Europe.³

• C. 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,^{4, 5}

may be a general feature of ageing nervous systems which need to be taken into account by those designing the environment in which we live, to make it friendlier to elderly inhabitants. This is an area for multidisciplinary research and cross-talk between neuroscientists and engineers. Other changes, such as problems with recent memory⁵ and focusing of attention, may result from accelerated neurodegeneration, and may be ameliorated by new drug treatments. Some treatments may slow down the pace of degeneration, others may compensate for existing deficits. In both cases, a rational drug development process requires a better understanding of the neurobiology of the ageing brain, both at the cellular and the systems level.

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 which have, in turn, led to disappointing therapeutic trials, eg trials for oestrogens as neuroprotective agents.

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 more reliable diagnostic tools are needed to differentiate normal ageing from age-associated pathological processes. In addition, new surrogate markers are required to enable critical follow-up of treatment efficacy in patients with neurodegenerative disease.

• D. Significance of increased research

Dopaminergic drugs have greatly improved the lives of elderly patients suffering from Parkinson’s disease, while cholinergic drugs have allowed patients with Alzheimer’s disease to stay at home for longer. However, there are no pharmaceutical or other therapies available for people with “normal”, age-associated memory problems which 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 6: STEM CELL RESEARCH: FROM APPLICATION IN HUMAN DISEASE TO BASIC MECHANISMS

W. Oertel – neurologist and neuroscientist, G. Höglinger – neurologist and neuroscientist, A. Bjorklund – basic neuroscientist

- A. 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) 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.

- B. 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 Parkinson's and Huntington's diseases as model disorders.¹ 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.² European researchers are starting to unravel the mechanisms and significance of neurogenesis as it occurs in the normal³ and diseased brain of adult mammals, including humans.⁴ The foundations for the study of the contribution made by haematopoietic stem cells to brain diseases have been laid in Europe.⁵ 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.

- C. 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,^{1 2} and therapeutic modulation of endogenous neurogenesis in the adult brain.^{3 4} For the first strategy, a detailed understanding of basic stem cell biology is needed if researchers are to control the induction of particular cellular phenotypes. 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.^{3 4} This is best studied with stem cells grown in culture. Based on such an approach, innovative strategies aimed at therapeutic manipulation of endogenous stem cells within the living brain by systemic pharmacological means⁴ or by gene therapy³ 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.⁵ 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. For example, their contribution to the inflammatory processes that initiate or aggravate neurodegeneration is unclear. The study of their contribution to such processes might offer innovative targets for therapeutic intervention. In addition, upon genetic modification, haematopoietic stem cells could act as Trojan horses for delivering large molecules such as growth factors directly to sites of ongoing neurodegeneration, neuroinflammation or other types of brain disease.

- D. Significance of increased research

The systematic study of stem cells in the context of neuroscience 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 neuropsychiatric diseases. Tens of millions of affected European citizens stand to gain from advances towards a cell-based treatment of neuropsychiatric disorders.

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6.2 MIND-BRAIN RELATIONSHIP AND MENTAL DISORDERS

Section editor: Julien Mendlewicz (ECNP)

THEME 1: FROM MOOD DISORDERS AND NORMAL MOOD TO ANIMAL MODELS, SIGNALLING MECHANISMS AND GENETICS

R. Corradetti – basic neuroscientist, G. Goodwin – psychiatrist, F. Holsboer – clinical scientist, R. Elgie – patient (GAMIAN Europe)

- A. Background

The lifetime prevalence for all mood disorders is between 5 and 10%. Unipolar depression is the most common diagnosis, showing a lifetime prevalence in women 2–3 times that for men, with a mean age at onset in the range 25–35 years. The most serious mood disorder, bipolar disorder, in which recurrent episodes of mood elevation may be interspersed with depression, has a lifetime prevalence of about 1%. 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 WHO to be the leading cause of disability in the world by 2020.

- B. Past achievements in Europe

The classification and recognition of mood disorder has essentially European origins and the boundary between unipolar and bipolar disorder is being redefined in large part on the basis of European epidemiology. In recent years, European scientists have contributed the first example of a valid genetic model of emotionality¹ and have completed cooperatively some of the largest genetic association studies to date, to establish the role of different polymorphisms in the aetiology of depression.^{2 3} The investigation of the role of stress hormones and the application of cognitive neuroscience to better 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 or cognition could inform the development of new medicines. A trans-European approach is essential in areas where expertise is distributed and the recruitment of large patient numbers or smaller samples of rarer disease sub-types is desirable. For example, the FP6 programme NEWMOOD, which involves 13 groups in 10 countries, investigates the changes in gene expression common to different animal models of depression, to develop new tools for personalised diagnosis and treatment.

- C. Proposal

Genetic predisposition, developmental and/or nutritional deficit, early life experience, chronic stress and drug abuse have been identified as factors contributing to vulnerability to depression.⁴ Investigation of animal models must continue to play a critical part in how we understand the stress-regulating systems of the brain and neurotransmitter systems that provide potential drug targets, as well as how treatments with “classic” and/or newer antidepressant drugs bring about adaptive changes in those systems. However, 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. It is increasingly recognised by the pharmaceutical industry that the introduction of experimental medicine models at the interface between Phase 1 and Phase 2 clinical trials is the way forward in this area. These would provide a rapid Go/No-Go signal, thus 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. Indeed, human tests of emotional processing may go well beyond what is currently possible in rodents to address perceptual and cognitive aspects of emotion perhaps unique to man, such as the interpretation of the emotional content of the facial expressions of others.⁵ More neuropsychologically informed human models could have a highly significant impact on drug development. This could be a strong focus for European centres which have an interest in the genetic investigation of depression, something that is already supported co-operatively in Europe.

Large scale clinical trials are most needed for bipolar disorder. As for unipolar disorder, there are several reasonably effective treatments for the acute and stabilisation phases of the disorder. The main clinical uncertainty concerns long term maintenance. For almost 30 years lithium carbonate has been the standard maintenance treatment, however it is not completely effective and it has a narrow therapeutic index. Uncertainty about lithium has been increased by the emergence of alternative drug treatments, such as valproate, lamotrigine and the atypical antipsychotics. The lack of efficacy of monotherapy has led to frequent use of combination treatments in the long term. We lack controlled data to guide clinician and patient choice between different monotherapies and combinations. In addition, bipolar disorder is now a broader diagnosis including, as bipolar II or spectrum cases, many patients who would formerly have been treated for unipolar depression. This poses a further fundamental problem only answerable by pragmatic clinical trials: should we use antidepressants or anticonvulsants to manage bipolar depression? The BALANCE trials are multi-site, cross-national studies, funded independently of industry, which are designed to answer such questions. Finally, psychotherapy is often the preferred treatment of patients with depression, and as genomics has shaped physical treatments, so it may shape the choice of psychotherapies in future.

- D. Significance of increased research

Despite the progress made in the last 50 years in understanding the function of neurotransmitter systems in mood disorders, we are far from having a convincing account of the causes of depression. Vertical integration of basic science, genetics and clinical research is increasingly possible, but 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 could improve our currently crude diagnostic classifications and, with advances in pharmacogenetics, bring forward an era of personalised medicine. We anticipate more efficient prediction of individual treatment response to medicines or psychological treatment. 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 most critically for guiding patient choice between different treatments working alone or in combination.

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THEME 2: FROM ANXIETY DISORDERS, FEAR AND AVOIDANCE TO ANIMAL MODELS, SIGNALLING MECHANISMS AND GENETICS

D. Nutt – psychiatrist, R. Corradetti – basic neuroscientist

- A. Background

Recent data on the epidemiology of anxiety and other brain disorders collected under the auspices of the European Brain Council and the European College of Neuropsychopharmacology show that up to 40% of the population will experience anxiety in their lifetime, as defined by clinical criteria.¹ Because anxiety disorders start early in life (the average age of the first episode is 15) and are both long-lasting and under-treated, they represent a huge burden on the individual and on society. The cost of anxiety disorders in Europe was recently estimated at €40 billion.²

- B. Past achievements in Europe

European groups have contributed much to research on anxiety disorders, especially in the identification in both mice and humans of genes and polymorphisms that predispose to anxiety. The molecular biology of GABA-A receptor subtypes involved in anxiety was worked out by teams in the UK and Switzerland, and the first receptor subtype-selective drugs were designed in the UK. Some of the definitive studies demonstrating the utility of antidepressants and anticonvulsants in the treatment of anxiety disorders were done in the UK, the Netherlands and Germany. Many of the researchers currently working on the brain mechanisms of anxiety are based in Europe (eg in the UK, The Netherlands and Estonia). The use of cognitive behavioural therapy (psychotherapy) approaches to treatment of many anxiety disorders was pioneered in the UK. However, although anxiety disorders are very common, they are also often co-morbid with each other and with other non-psychiatric disorders, so finding pure populations

for study is a difficult and slow undertaking. A trans-European approach would greatly accelerate this process.

- C. Proposal

Basic aspects

We need a fuller understanding of the role of neurotransmitter systems in the functioning of the central nervous system, their dysregulation in animal models of anxiety and panic disorders, and their interplay with hormone and peptide neurotransmission.³⁻⁵ 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 to help define genes predisposing to anxiety in animals and humans. It will 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 (positron emission tomography and single photon emission computed tomography) 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 of 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, so 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 and the risk of withdrawal reactions.

(4) To optimise the use of drug and psychotherapy treatments either alone or especially in combination, to maximise the likelihood of patients reaching a state of full functional recovery (remission).

Bi-directional collaboration and coordination: Because anxiety is such a universal phenomenon there is generally good correlation between the findings in preclinical, animal models and in human studies, so the two approaches have developed in an integrated fashion. However, the latest data on the value of antidepressants in treatment of human anxiety have yet to be properly evaluated in preclinical models, so their mode of action is still relatively obscure and requires further investigation.

- D. Significance of increased research

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

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THEME 3: FROM ADDICTION AND NORMAL PLEASURE-SEEKING TO ANIMAL MODELS, SIGNALLING MECHANISMS AND GENETICS

W. van den Brink – psychiatrist, A. Zimmer – basic neuroscientist, J. Smith – industry (Eli Lilly)

- A. 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 for Europe which has been estimated at almost €60 billion a year.¹

- B. 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^{2,3}; genetic research using twin registers⁴; animal studies using gene-expression and knock-out strategies and studies with humans combining investigation of polymorphisms with neuroimaging. European industry has developed new, effective pharmacological treatments for addiction (such as acamprostate 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 co-prescription 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 co-morbidity 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, multi-centre 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.

- C. Proposal

On the basis of animal models and neuroimaging 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 to wanting and from ventral striatum processes to dorsal striatum processes.²

The genomics of addiction encompass both inherited determinants of addictive behaviour and the effects of drug taking on gene expression. Genetic factors seem to explain 40 to 60% of overall vulnerability to addiction, and allelic variations in several genes—for example, in dopaminergic, glutamatergic and glucocorticoid receptor genes—are likely to contribute to this. One of the more productive areas 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 the whole systems levels. Behavioural tasks can be used to link the gene manipulation directly to measures of dependence. Random germline mutations can be introduced into the genome at high frequency using a chemical mutagen, ethylnitrosourea (ENU), and several large scale ENU mutagenesis efforts are currently underway. This technique permits the discovery of new and unexpected targets.

The key clinical questions in the addiction field concern the meaning of basic findings for human brain function, which can be studied using neuroimaging techniques and is giving rise to a better understanding of the brain as an integrated machine with compensatory mechanisms; understanding of the mode of action of current treatments, and calculating 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. Finally, genetic findings may lead to genetics-based patient-treatment matching and hence more effective interventions.⁵

- D. 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 4: FROM SCHIZOPHRENIA AND NORMAL THINKING TO ANIMAL MODELS, SIGNALLING MECHANISMS AND GENETICS

D. Naber – psychiatrist, G. Innocenti – basic neuroscientist, K. Alptekin – patient (GAMIAN Europe)

- A. 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).¹ 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.

- B. 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.^{1,2} 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.² Functional studies have pointed to underlying disorders of cortical dynamics resulting from subtle changes in cortical connectivity.² The search for genes specifically affected in the schizophrenic brain has identified a number of candidate genes.^{3,4} 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 co-selected with genes responsible for the lateralised structure and function of the human brain.⁵

- C. Proposal

Research on schizophrenia touches on several fundamental issues at the heart of basic and clinical neuroscience. These include the relationship between genes and environment in the building of neural circuits, the relationship between structure and function in the adult brain, the relationship between mind and brain and the position of man in the evolution of mammals. As a result, research on schizophrenia and research on the genetic, structural and functional basis of human brain development are highly likely to cross-fertilise one another. Understanding the pathophysiology of schizophrenia will help to clarify how the brain's neural circuits gives rise to cognition, perception and behaviour. 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. It is also a developmental disorder, so with this increased knowledge it might 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 supported in parallel:

(1) Identify affected genes in families having a patient with schizophrenia. Several such candidate genes are currently being studied^{3,4}

(2) Investigate the function of those genes in animal models using targeted mutagenesis and phenotyping of the models at the system level

(3) Consolidate existing data on the neuropathology of the human schizophrenic brain by promoting the development and/or merging of European brain banks

(4) Investigate the functional circuits of the schizophrenic brain by combining imaging techniques with high temporal resolution (electroencephalography or magnetoencephalography) with techniques with high spatial resolution (functional magnetic resonance imaging) and others with high molecular/pharmacological resolution (positron emission tomography)

(5) Link the results of animal studies on mutated genes to the pathophysiology of schizophrenia by analysing selected neural circuits in animals and man with comparable techniques

(6) 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.

- D. 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 5: FROM HUMAN SLEEP DISORDERS TO ANIMAL MODELS, SIGNALLING MECHANISMS AND GENETICS

M. Billiard – neurologist, A. Borbély – basic neuroscientist, P. Linkowski – psychiatrist, P. Morselli – patient (GAMIAN Europe), J. Gibbs – patient

- A. Background

The latest version of the International Classification of Sleep Disorders¹ cites eight categories of sleep disorder: insomnia, sleep related breathing disorder, hypersomnia not due to a sleep related breathing disorder, circadian rhythm sleep disorder, parasomnia, sleep related movement disorder, isolated symptoms and other sleep disorders, which in turn comprises 75 individual sleep disorders. The incidence of insomnia in the general population is estimated at 36%, with 27% suffering occasionally and 9% chronically. Between 4 and 6% of the general population is affected by severe hypersomnia, while between 40 and 80% of shift workers experience sleep disorders. Sleep disorders impact on quality of life and have adverse consequences ranging from impaired cognitive function to increased mortality. The total cost of sleep disorders in Europe as a whole has not recently been calculated. However, the cost of insomnia alone, in France in 1995, has been estimated at around €1.6 billion.

- B. Past achievements in Europe

Treating sleep disorders, as opposed to treating their symptoms, requires both a basic knowledge of sleep and an insight into the pathophysiology of these disorders. Among past European achievements in basic sleep science are studies on the neurobiology of sleep²; development of models of sleep regulation based on various circadian indexes and on all-night spectral analysis of sleep electroencephalography (EEG);³ molecular approaches to isolating sleep-related genes⁴ and neuroimaging studies involving functional magnetic resonance imaging and receptor imaging (5-HT, ACh, GABA).⁵ On the clinical side, progress has been made using animal models of sleep disorders—mostly dogs, mice and *Drosophila*; EEG

spectral analysis; pharmacological and biochemical studies; genetic studies in both single case and multiplex families and studies using neuroimaging techniques. However, one of the main difficulties with clinical studies is finding appropriate population samples that are clinically well-defined. European cooperation is crucial if we are to ensure future advances in this area.

- C. Proposal

Natural animal models of some sleep disorders are already known, including canine narcolepsy, sleep-disordered breathing in English bulldogs and circadian rhythm sleep disorder in *Drosophila*. However, such models are lacking for insomnia, idiopathic hypersomnia, recurrent hypersomnia, sleepwalking and night terrors, restless legs syndrome and periodic limb movement in sleep. Efforts should be made to find or develop animal models for these disorders.

In humans, EEG sleep patterns including sleep stage distribution and quantitative description of the sleep process, have been investigated in the general population and in twins. However, very few systematic studies have been carried out in people with sleep disorders, and more such studies are needed. Single gene sleep disorders are rare. Most sleep disorders are complex phenotypes regulated by many genes, gene interaction, environmental factors and gene-environment interaction. Multiple approaches using both animal models and humans are necessary to disentangle the biological basis of these disorders.

On the genetic side, animal models are crucial for the discovery of new genetic mutations or polymorphisms. The genome-wide scan is the method of choice for discovering new, relevant genes, however a complementary approach is the study of candidate genes, which can help determine whether a gene that is already known is implicated in the disruption of sleep regulation. The study of genetically modified mice has a particularly promising future. One good example is the knock-out mouse for the pre-prohypocretin gene, whose phenotype resembles human narcolepsy. The quantitative trait loci approach consists of identifying all the loci that control a quantitative trait that gives rise to variation between two strains of inbred mice. It is particularly appropriate when the trait is complex and the number of genes high. In humans, two approaches might be considered in an attempt to localise genes implicated in sleep disorders: genetic linkage studies of a large number of multiplex families affected by a defined disorder, or association studies (based on candidate genes) of a very high number of single case families.

The role of the environment in sleep disorders has been somewhat neglected. In animals, the methodology for studying possible environmental influences should include the use of enriched versus non-enriched environments, as well as environmental light/dark cycles and environmental chemicals and noise. In humans there are very few solid studies on the environmental factors involved in the development of most sleep disorders. There is therefore an urgent need to develop structured questionnaires designed to collect reliable data on demography, medical and family history, psychological profiles and life events exposure, both in patients with sleep disorders and in matched controls.

All these research approaches require bidirectional collaboration and coordination between basic researchers working in animal models and humans, and clinicians who can provide both index cases with preselected clinical features and multiplex families, all of whom have completed extensive structured questionnaires.

- D. Significance of increased research

The potential clinical impact of this proposed research is difficult to measure as yet, but the discovery of new genetic

factors with a major influence on sleep disorders will certainly inform the search for new therapeutic strategies. The role of environmental factors in the development of sleep disorders must also be considered, with a view to preventing or delaying their onset. There is no doubt that increased research in this area would benefit a significant proportion of the European population.

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THEME 6: FROM EATING DISORDERS AND OBESITY TO BRAIN MECHANISMS OF APPETITE REGULATION

R. Adan – pharmacologist, A. Tataranni – industry (Sanofi), S. Bloom – basic neuroscientist

• A. Background

Obesity now accounts for approximately 400 000 deaths per year in the US and obesity is an increasing problem in Europe. Of the 77 million children living in the European Union, 14 million are overweight and will become obese adults, exacerbating the problem still further. The obesity epidemic has adverse economic consequences too. Obesity is responsible for between 5 and 7% of the total annual medical expenditure in the US, or \$75 billion per year, and expenditure on obesity is rising fast. Annual indirect costs of obesity, mainly resulting from loss of economic productivity, are estimated at \$64 billion, so that the total costs of obesity (direct and indirect) may now be as high as \$139 billion per year in the US.¹ Eating disorders such as anorexia nervosa have a lower incidence (8 new cases per 100 000 people per year) and affect mainly young females, but among the psychiatric disorders they have the highest mortality rate. The aetiology of eating disorders is unknown and there is no standard treatment or pharmacotherapy available for them.

• B. Past achievements in Europe

Several European Union research programmes have tackled the problems of obesity and eating disorders. European researchers have described the role of neuropeptides in regulating human energy balance in the context of food intake² and have also identified genes that contribute to susceptibility for obesity and anorexia nervosa.^{3,4} However, most of the research conducted to date has not focused on the role of the central nervous system. It is clear that obesity is due to an eating drive 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 contribute to the development of obesity and eating disorders, and Europe with its cultural diversity and different eating habits provides an excellent research opportunity for determining risk factors and identifying possible dietary interventions. What is needed is a coordinated network of research activities among the strongest European neuroscience groups working on mechanisms of appetite regulation.

• C. Proposal

Both obesity and eating disorders are multifactorial, heterogeneous diseases with a strong genetic component. Since the

discovery of leptin in 1994,⁵ 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, yet current drugs for obesity, such as sibutramine and rimonabant, have mechanisms of action that are based on old concepts. They were not discovered as a result of this new understanding of appetite, satiety and reward. In the coming decade research will further elucidate the neural circuits and neurotransmitters that are implicated in obesity and eating disorders, and in so doing generate new therapeutic strategies, including drugs. For that to happen we need new, advanced animal models in which the behavioural traits associated with food intake can be dissociated, and the role of individual genes and neurotransmitters in determining those traits identified. European researchers working on genetically modified rodents, neurogenomics, proteomics and advanced animal models must come together in a multidisciplinary, collaborative network to discover the neural mechanisms underlying obesity and eating disorders. By combining epidemiological, genetic and neuropsychological approaches, they will be better equipped to determine the extent to which such behavioural traits contribute to human obesity and eating disorders.

• D. Significance of increased research

The aetiology of obesity differs between patients, and therefore its treatment should be tailored to the individual patient. Research on the mechanisms underlying obesity is essential if we are to devise individualised therapies. For eating disorders such as anorexia nervosa, the aetiology is largely unknown and there is no standard therapy or drugs. A better understanding of the mechanisms underlying these disorders will provide new avenues for therapeutic intervention.

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THEME 7: FROM OBSESSIVE-COMPULSIVE DISORDERS AND NORMAL CAREFULNESS AND CLEANLINESS TO BASIC MECHANISMS OF SUCH PERSONALITY CHARACTERISTICS

B. Nuttin – neurosurgeon, P. Morselli – patient (GAMIAN Europe), J. Zohar – psychiatrist

• A. 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.¹ Typical age of onset is late teens, and both sexes are equally affected. The patient is well 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. Typical patients spend several hours a day

engaged in these endless obsessions and/or compulsions, which leads to reduced productivity and lower academic achievement.

- B. 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,² and was later confirmed by large, double-blind, placebo-controlled studies. These studies established serotonin (5-HT) as a therapeutic agent, but they also showed that it played a role in the pathogenesis of the disorder.³ More recent studies point to a role for the genetic polymorphism associated with 5HT_{1D},⁴ as well as specifying the associated brain circuitry.⁵ 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 clues as to what can be done for these patients, data is scarce. To date no trial has been conducted to look for biological markers of the disease in a sufficiently large number of patients for whom the family and personal history is known.

- C. Proposal

We propose to conduct a naturalistic, open-label study in OCD patients in Europe. This would involve centres where there are academically active OCD clinics— for example, at the Universities of Florence, Utrecht and Tel Aviv. With each centre providing around 100 patients, such collaboration would generate a large sample size and enable us to test the predictive power of well-established biological markers whose clinical utility in prediction of response to pharmacological interventions has not been explored. These markers are: 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 then be given open treatment with a selective serotonin reuptake inhibitor (escitalopram), a well-established anti-obsessive treatment, and monitored carefully. After two months they will be re-evaluated using the Yale-Brown Obsessive-Compulsive Scale (YBOCS) as a primary measure. Drug compliance will be evaluated by pill counts and blood tests. There are no serious adverse effects of the 5-HT challenge proposed, and the expected transient exacerbation of symptoms that might occur during these challenges, or during the behavioural challenge that is given prior to brain imaging, are not different from the OCD symptoms these patients endure during their routine daily activities. Non-responders, as defined by a decrease of less than 35% in their YBOCS score, will be compared to responders (decrease of 35% or more in their YBOCS score) in terms of their initial response to the behavioural challenge and to the corresponding 5-HT challenge, as well as in relation to a family history of tics, OCD, other anxiety disorders, affective disorders or schizophrenia and past history of attention-deficit/hyperactivity disorder. DNA samples will also be analysed for 5-HT_{2D}, other 5-HT receptor subtypes and dopamine markers.

- D. Significance of increased research

This study could help to identify the biological basis for a lack of response to anti-obsessive treatment in OCD patients, as it might be expressed by differential patterns of brain activation (following an appropriate behavioral challenge) or by differential response to 5-HT challenge. Both 5-HT_{1D} and 5-HT_{2C} 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. If the underlying mechanisms of OCD were known, we could begin to explore alternative therapeutic approaches for those one million OCD patients in Europe who do not respond adequately to treatment. Progress here 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 benefits for patients, their families and society at large.

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THEME 8: FROM COMA, VEGETATIVE STATE AND BRAIN DEATH TO MECHANISMS OF ALERTNESS

E. Schmutzhard – neurologist, H-C. Pape – basic neuroscientist, J. Pickard – neurosurgeon

- A. 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. Costs incurred by traumatic brain injury, the main cause of disability in young people, exceed billions of euros per year in Europe.¹ 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 widespread areas of the thalamus and the cerebral cortex. The ascending networks exert their influence through 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 vegetative state and/or brain death.

- B. Past achievements in Europe

The concept of the ascending reticular activation system was introduced by two Italian neurophysiologists, Moruzzi and Magoun, as early as 1949. In the early 1970s, Jouvet significantly extended the basic concept through the identification of multiple networks that use biogenic amines as neurotransmitters for the control of wakefulness.² 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 the theoretical and physiological grounds. 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 multi-society taskforce nicely summarised the medical aspects of persistent vegetative state, European researchers published the first hints as to how to predict recovery from non-traumatic coma, post-traumatic coma and vegetative state.³ Further evaluation of cerebral function in coma, vegetative state, locked-in syndrome, minimally conscious state and brain death has been carried out by Belgian researchers.⁴

- C. 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 (vegetative state). We need a better understanding of the pathophysiological processes that lead to these conditions, and 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 vegetative state, minimally conscious state and brain death.

Hypoxic brain damage and traumatic brain injury are the two main causes of impaired consciousness, coma and vegetative state. 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 multi-centre project is needed to improve our understanding of the underlying pathophysiology through the study of biochemical and inflammatory processes in traumatic brain injury and cerebral hypoxia, including studies of brain function (using magnetic resonance imaging (MRI)) and metabolism (using positron emission tomography (PET), single photon emission computed tomography (SPECT), functional MRI and microdialysis) in these disease states.⁴ Specifically, such a project should:

(1) Explore qualitatively and quantitatively the extent of functional impairment in comatose and vegetative state patients using PET and SPECT.

(2) Study prospectively therapeutic interventions such as hypothermia, osmotic therapy or 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. There is currently a lack of animal models of traumatic brain injury which allow for the translation of mechanistic findings into neuroprotective and neuroregenerative treatment for humans. The most widely used animal model of traumatic injury, the lateral fluid percussion model, was developed more than 15 years ago, and its validity has been compromised when attempts have been made to translate findings to severely injured patients.⁵

(7) Explore the exciting possibility of using transgenic and mutant mouse models. The overall aim with these animal models is to study mechanisms of brain injury—mechanisms that cannot be studied in the clinical setting—and hence to provide a foundation for the development of novel therapeutic interventions.

- D. Significance of increased research

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

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THEME 9: FROM VIOLENCE AND CRIME TO BRAIN MECHANISMS OF AGGRESSION

M. Kruk – behavioural neuroscientist, J. Haller – behavioural neuroscientist

- A. Background

Violence represents a terrible and costly burden on society. Only a fraction of the population is criminally violent, but violence is a low frequency, high impact behaviour. It produces profound changes not only in the victims and the offenders, but also in witnesses. Indirectly, therefore, it affects the very structure of society by limiting the freedom of action of many. Moreover, a significant number of victims of violence become perpetrators later on. Why this should happen to some individuals and not others is poorly understood, but recent advances, both conceptual and technological, have enabled investigations into how genetic predispositions and social stressors at critical phases in development interact to produce individuals who are easily provoked to violence. Both animal and human studies suggest that the brain mechanisms that control aggressive behaviour are activated rapidly during social conflict. Animal research also suggests that social stressors produce lasting changes in those same mechanisms. Such changes apparently reduce an individual's capacity to deal adaptively with future social conflicts, and renders vulnerable individuals more prone to violence.

- B. Past achievements in Europe

Research on aggressive behaviour and animal conflict has deep historical roots in Europe. Two Nobel Prize-winning founders of animal behaviour studies, Konrad Lorenz and Niko Tinbergen, conceived of aggression as an adaptive behaviour essential to individual and species survival.^{1 2} Pierre Karli viewed aggressive behaviour as an individual characteristic that is shaped by the concerted influence of experience, environment and hormones on brain mechanisms involved in anxiety, flight, avoidance and reward, during critical periods in development.³ Later, French and Dutch research groups

successfully selected for aggression in mice, and studied its physiological and genetic basis in high and low aggressive mice.⁴ From those studies it became clear that deviations in both form and target of aggressive behaviour would be useful markers of pathology. A Hungarian-Dutch research group recently identified the critical role of adrenocortical stress hormones in social conflict.⁵ Such stress hormones produce a long-lasting change in the balance between fight and flight behaviour, and accompanying changes in brain structures involved in anxiety, stress regulation and aggression. Recent studies in humans have revealed that maladaptive aggressive behaviour in several psychopathologies is often accompanied by a disturbance in the regulation of the adrenocortical stress response, supporting this hypothesis. A history of severe psychological trauma has proved an important contributing factor. Taken together, these findings suggest that violence is the outcome of an interaction between individual vulnerability and the influence of the environment during critical stages of development. There are strong indications that hormonal feedback to the brain is crucially involved in such an interaction. Such feedback probably affects the expression of certain genes in brain structures that control violence.

- C. Proposal

There is a need to clarify the brain mechanisms involved in the development of maladaptive aggression and violence, and to identify targets for more effective therapies. Understanding human psychopathology in violent individuals is not an easy task. Affected individuals constitute a vulnerable, poorly accessible group. Moreover, the episodic nature of many of the symptoms hampers systematic studies, and biological state and trait markers are not yet available. On the other hand, most of the brain mechanisms involved in the control of aggression are phylogenetically old and well-preserved in mammals. Animal models of both adaptive and pathological aggression can be used to identify and trace the interactions between brain mechanisms involved in the control of aggression. Gene expression in critical brain areas, that is triggered by social conflict or by certain hormonal conditions, should provide clues to the mechanisms that underlie a shift towards maladaptive social conflict resolution.

The ongoing, parallel search for individual variation in genes conferring vulnerability and resilience to aggression in specific human populations will yield a set of candidate genes to be matched with the results of gene expression profiles obtained from animal research. Special attention should be paid to the specific nature of the aggressive symptoms in humans, since different underlying psychopathologies may produce different forms of maladaptive conflict resolution. Similar attention should be paid to gender differences in aggression.

Models of animal aggression will also provide clues to changes that occur in the brains of violent humans, when combined with increasingly powerful imaging technologies. Experimental interventions can be tested in validated animal models that have successfully been used to assess drug and hormone effects in different forms of aggressive behaviour. Animal studies show that the same intervention in brain or hormonal mechanisms may produce different effects in different aggression models, so attention must be paid to the specific nature of the change produced by any intervention if this research is to lead to effective therapeutic interventions.

- D. Significance of increased research

European history has shown that it often takes only a few violently inclined individuals in highly visible positions to disrupt the social structure of an otherwise peaceful community—especially in times of social and economic stress. Much is therefore to be gained by the study of mechanisms involved in the pathogenesis of violent behaviour.

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6.3 DEGENERATION AND REPAIR IN THE BRAIN

Section editor: Manfred Westphal (EANS)

THEME 1: FROM ALZHEIMER'S DISEASE AND OTHER DEMENTIAS TO BASIC MECHANISMS OF NEURODEGENERATION

G Waldemar – neurologist, M West – basic neuroscientist, A Nordberg – geriatrician, I. McKeith – psychiatrist, J Georges – lay person (Alzheimer Europe)

- A. Background

Alzheimer's disease, the most common cause of dementia, 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. Dementia may affect adults of all ages, but the risk increases with age. According to European epidemiological studies, dementia affects 6 to 7% of the population above 65 years of age.¹ In Europe (the European Union, Iceland, Norway and Switzerland), the estimated number of patients with dementia of 65 years and over is 4.9 million, with an estimated annual incidence approaching 1 million.^{2–3} More than half of these patients have Alzheimer's disease. As Europe's population ages, these numbers are expected to increase dramatically. The costs related to dementia healthcare amount to €55 billion per year in Europe, most of which is spent on long-term institutional care.³ But importantly, this figure does not include the very high indirect costs associated with the contribution of caregivers, since the majority of patients with Alzheimer's disease live at home and are cared for by relatives and friends. The human costs of the disease are incalculable, but Alzheimer's disease ranks second among the brain diseases in terms of the burden of disease in Europe.⁴

- B. Past achievements in Europe

The pathological features of Alzheimer's disease include extracellular plaques containing beta-amyloid, intraneuronal neurofibrillary tangles containing abnormally phosphorylated tau protein, neuronal cell death, inflammatory processes, glia and microglia activation, and neurotransmitter disturbances. European researchers have played a major role in the genetic, neuropathological and neuroimmunological studies that have helped reveal the pathogenic pathways underlying Alzheimer's disease. There is now strong evidence that a rise in brain amyloid levels is involved in the initiation of the disease. This forms the basis of the beta-amyloid cascade hypothesis. Large European epidemiological studies have been crucial for mapping the medical and social risk factors and the preclinical symptoms in Alzheimer's disease. There is accumulating evidence that Alzheimer's disease has a very long preclinical phase. For example, episodic and visual memory tests can predict Alzheimer's disease more than a decade before the clinical diagnosis. European research groups have pioneered the development of cerebrospinal fluid and neuroimaging biomarkers for early disease identification, and for disease

modification. Finally, several European biotechnology and pharmaceutical companies, as well as university-based research groups, have contributed to the basic development of novel, disease-modifying therapeutic strategies, which are now in early clinical development.

- C. Proposal

Despite major progress in our understanding of the early symptoms and causes of dementia, and the introduction of symptomatic drug therapy for Alzheimer's disease over 10 years ago, the biological basis of Alzheimer's disease is not fully understood and there is no known cure. For a breakthrough towards finding a cure, we need to be able to detect the disease in its preclinical stage, and to initiate effective treatment prior to the development of significant pathology. Early detection will most likely rely on a combination of novel biomarkers (based on proteomic, transcriptomic and metabonomic analyses of biological samples) combined with neuropsychology and neuroimaging. 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 be crucial for the development of new therapeutic approaches. Salient features of that integration should include:

- (1) A common goal of uncovering the molecular mechanisms involved in Alzheimer's disease
- (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 neuroimaging 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-Alzheimer's disease dementias, such as fronto-temporal 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 for them, but also to the discovery of new elements in the pathogenesis of Alzheimer's disease, and 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 Alzheimer's disease, and to develop ways of preventing, slowing or ameliorating its symptoms. The EADC provides an excellent basis for the coordination of European clinical studies.

- D. 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 the doubling of prevalence figures for each successive five year age band after the age of 65, delaying the onset of the disease by five 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 Alzheimer's disease is feasible, and we believe that the European research community can make a significant

contribution to that goal within the next six years. It may even be achieved within a decade. The increased research will have important implications for other neurodegenerative dementia disorders too, and the initiatives will produce innovative results that could form a foundation for productive interactions between governments and the private sector in the form of technology transfer.

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THEME 2: FROM PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS TO THE CURE OF BASAL GANGLIA DEGENERATION

P. Calabresi – neurologist, W. Oertel – neurologist and neuroscientist, T. Isaacs – patient (European Parkinson's Disease Association)

- A. Background

Parkinson's disease 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. Non-motor complications of Parkinson's disease may have an equal or greater impact on some patients. These include cognitive impairment and autonomic, sleep and sensory disturbances. It has recently been estimated that in the US, total medical care costs for patients with Parkinson's disease are US\$23 billion annually. This estimate is higher than most previous estimates, with implications for healthcare delivery systems worldwide.¹ As the population of Europe ages, the costs of Parkinson's disease are progressively increasing.

- B. Past achievements in Europe

European scientists discovered the dopamine deficit in Parkinson's disease and clearly lead research on clinico-neuropathological relationships in the disease. They have contributed significantly to the discovery of the mutations involved in familial forms of Parkinson's disease, enhancing the understanding of the pathogenesis of both genetic and sporadic forms of the disease. Their research suggests that deficits in mitochondrial function, oxidative stress, the accumulation of aberrant or misfolded proteins and ubiquitin-proteasome system dysfunction may be the principal molecular events underlying sporadic and familial forms of Parkinson's disease.² 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.³ The majority of animal models for basic research on Parkinson's disease and current symptomatic pharmacotherapy are based on European discoveries. Of the latter, levodopa (L-dopa) is still considered the most effective treatment for Parkinson's disease. However, the shortening duration of the

L-dopa effect (end-of-dose akinesia), the onset of involuntary movements (dyskinesia) and dopaminergic-induced psychosis are debilitating side effects that are associated with prolonged L-dopa administration in virtually all Parkinson's disease patients. European research has shown that the neural substrate of L-dopa-induced dyskinesia includes profound changes in the interplay between dopaminergic and glutamatergic transmission in the basal ganglia circuitry, leading to aberrant synaptic plasticity.⁴ Imaging of central nervous system (CNS) structure and function in Parkinson's disease is well-developed and has assisted European neuroscientists in making major contributions to the development of cell replacement strategies for Parkinson's disease therapy, by employing primary dopaminergic neuroblasts.

● C. 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 neuroimaging
2. The building and use of clinical, genetic and imaging databases to allow the identification and validation of biological markers 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 Parkinson's disease and the identification of gene-environment interactions in Parkinson's disease pathogenesis
3. Identification of preclinical diagnostic measures 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 Parkinson's disease patients
5. Development of novel, chronic animal models for basic research
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 Parkinson's disease, but numerous hurdles remain to be overcome with stem cell therapy;⁵
9. Deciphering the cellular and molecular mechanisms of cell death within specific cell populations in Parkinson's disease and experimental parkinsonism as a basis for neuroprotective interventions
10. Identification of therapeutic proteins as well as targets for drug intervention. In particular, the possible role of trophic factors in the pathophysiology of Parkinson's disease, and their potential role in its treatment, should be further explored
11. Characterisation of the molecular mechanisms leading to L-dopa-induced dyskinesia, with the aim of blocking its development
12. Studies on mechanisms of non-motor symptoms and on their treatment
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 etiology, pathogenesis, diagnosis and therapeutical developments, as no effective treatment is yet known for these disorders.

● D. 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 Parkinson's disease 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 Parkinson's disease. 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 Parkinson's disease.

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THEME 3: FROM STROKE TO BASIC MECHANISMS OF ISCHAEMIA AND PROGRAMMED CELL DEATH

W. Heiss – neurologist, P. Schmiedek – neurosurgeon, A. Hagen – patient (Stroke Alliance for Europe), W. Eisert – industry (Boehringer Ingelheim)

● A. Background

Acute stroke is characterised by the sudden onset of focal neurological deficits of variable nature and severity. Acute cerebrovascular diseases (CVD) 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, the acute CVD are classified as ischaemic strokes (68 to 80%), spontaneous intracerebral haemorrhages (7 to 20%), subarachnoid haemorrhages (1 to 7%) and sinus venous thromboses (1 to 2%). The remaining 2 to 15% cannot be classified due to lack of data. The prognosis varies according to this classification, with intracerebral haemorrhage incurring the highest mortality. 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.

● B. Past achievements in Europe

European stroke research centres have contributed a great deal to knowledge of the pathophysiology of CVD, especially to the understanding of the development and propagation of ischaemic cell damage and the concept of the penumbra,¹ which is 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.² 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 management of acute stroke in many European countries.³ 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 inhibitors⁴ and in evaluating the efficacy of endarterectomy for symptomatic and asymptomatic carotid stenosis.⁵ European neurosurgeons led the evaluation of early surgery for spontaneous intracerebral haematomas and the introduction of anti-thrombotic treatment for cerebral sinus venous thrombosis.

- C. 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 ischaemic damage. For that purpose, it is of the utmost importance to develop and implement 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. These models can then be used to evaluate therapeutic concepts and treatment effects. 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 which 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.

Further studies are needed to clarify whether stem cells that are injected after experimental occlusion of the middle cerebral artery, and which have been shown to migrate to an ischaemic lesion, can form connections and enhance neuroplasticity for improved recovery. The risk of tumour formation associated with experimental stem cell therapy must be investigated further, and the molecular mechanisms involved in this neoplastic transformation analysed in detail. Additional experiments are required to demonstrate the applicability of neurogenic stem cells for therapeutical purposes.

A special research programme should be established to study mechanisms of recovery after stroke, and to evaluate potential measures for improving rehabilitative therapy. We also need epidemiological studies to understand why the incidence of acute CVD and its associated mortality varies across Europe, which explore the differences in risk factors, prevention and management of stroke in different countries. Strategies must be developed to standardise diagnostic procedures and therapeutic strategies across all European countries and in rural as well as urban areas. This programme will require the broad involvement of the public and the continuous education of medical personnel involved in prevention and management of stroke.

- D. Significance of increased research

Stroke is the third most frequent cause of death in Europe, and a leading cause of disability. The benefits to patients, those who care for them and society in general of reducing the burden of stroke are therefore 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 isolated rural areas—have access to the gold standard of stroke care.

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THEME 4: FROM EPILEPSY TO BASIC MECHANISMS OF NEURONAL EXCITABILITY AND EPILEPTIC CELL DEATH

H. Klitgaard – industry (UCB), A. Pitkänen – basic neuroscientist, J. Schramm – neurosurgeon, H. Stefan – neurologist

- A. Background

Approximately 0.7 to 1% of the world's population, 50 million people, have epilepsy according to the World Health Organization. The annual incidence of epilepsy is 30 to 50 cases per 100 000 people, and incidence peaks in childhood and old age. A large proportion of patients therefore have the disease for most of their lives, and as the European population ages, the economic and social burden of epilepsy will increase markedly. Epilepsies can be divided into three categories based on aetiology: idiopathic, symptomatic and presumed symptomatic. In idiopathic epilepsies, genetic factors have a major causative role in the development of seizures. In symptomatic epilepsies, there is an identifiable lesion in the brain that triggers seizures (such as trauma, stroke or degenerative disease). Presumed symptomatic epilepsies are those which are likely to be symptomatic, but no lesion can be identified by the methods currently available. Epilepsy accompanies major brain diseases including traumatic brain injury, stroke and Alzheimer's disease, making the outcome of these diseases worse. Up to 20% of the costs of all neurological diseases are related to the treatment of epilepsies. The total annual costs (direct and indirect) related to treating epilepsies in the UK, for example, is £1.23 billion (€1.82 billion).¹

- B. Past achievements in Europe

European research has already had a significant impact on our understanding of epilepsy, including:

- (1) the genetics of epilepsy
- (2) the basic mechanisms of the development of epilepsy after brain insults
- (3) the effects of epilepsy on brain function
- (4) the diagnosis of epilepsy in patients using seizure semiology, and with the help of sophisticated imaging techniques such as magnetic resonance imaging (MRI); and both pharmacological and surgical treatment of epilepsy.^{2–4}

However, up to 30% of patients cannot be treated adequately with existing anticonvulsant drugs, due to poor efficacy or intolerable side effects. Five to 10% of all cases of epilepsy ultimately develop an intractable condition requiring them to be considered for surgery, and these patients also have an increased risk of injuries or sudden unexpected death (SUDEP).

- C. Proposal

Basic research

Researchers need to:

- (1) develop relevant models of epilepsy that can be used to investigate epilepsy syndromes in the immature and mature brain

(2) identify predisposing genes and their mechanisms in epilepsy

(3) characterise the molecular mechanisms that regulate the reorganisation of circuitry during the development of epilepsy, and the transformation of that circuitry from the non-epileptic to the epileptic state

(4) identify biomarkers, for example neuroimaging or cerebrospinal fluid markers, that predict risk of epileptogenesis, the progression of epilepsy and whether or not it will be refractory to drugs

(5) identify underlying reasons why some cases of epilepsy are refractory to drugs, including genetic factors

(6) search for novel treatments to repair epileptogenic neuronal alterations, such as stimulation therapies, gene therapy, cell transplantation and radiation.

Clinical aspects

A rational disease-modifying treatment requires knowledge of the key modulators of epileptogenesis. The delineation of the epileptogenic network in the brain has still not been resolved sufficiently. Especially in non-lesional, focal epilepsies, new diagnostic approaches using high spatial resolution functional imaging (MRI, functional MRI, spectroscopy, positron emission tomography and single photon emission computed tomography) in combination with high temporal resolution electrophysiological techniques⁵ (magnetoencephalography, electroencephalography and transcranial magnetic stimulation) could revolutionise non-invasive, presurgical diagnostics and allow the increasingly precise definition of both epileptogenic and function cortex. The investigation of autonomic changes in relation to prevention of SUDEP and psychiatric disorders are other important research topics. Because unsuccessful treatment may lead to progressive deterioration of the clinical condition including memory deficits, more effective anti-epileptogenic treatments must be developed. For epilepsy surgery, functional preservation after selective resection is another major challenge for the future. This should be based on determination of mental reserve capacities and multimodal functional neuronavigation, providing epilepsy surgery tailored to the individual. Factors that detract from patients' quality of life should also be identified, with a view to improving the well-being of patients who live with epilepsy.

Bidirectional aspects

The creation of expert networks in Europe, including medical, technological and information technology specialists, would help to advance our understanding of epilepsy. An interdisciplinary approach involving both basic and clinical researchers offers the possibility of exchanging creative thinking over diagnostic and therapeutic procedures, and creates a unique opportunity for exploring normal and abnormal brain function including reorganisation. If the epileptogenic zone can be precisely resected by epilepsy surgery, then basic researchers will be able to study the underlying mechanisms of epileptogenesis and epileptogenicity (seizure susceptibility) in human tissue, using methodologies that can not be applied in vivo to humans, and make useful comparisons with animal tissue.

• D. Significance of increased research

Possible benefits of this research to the individual include seizure control without side effects and improved social integration, for example in enabling patients to retain their driving licence, work productively and generally enjoy a better quality of life. Possible benefits to European society include reduced healthcare costs because more patients could be seizure-free and at the same time, increase their working capacity.

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THEME 5: FROM MULTIPLE SCLEROSIS AND OTHER INFLAMMATORY DISORDERS TO BASIC MECHANISMS OF NEURO-IMMUNOLOGY

R. Schlathau – patient (European Multiple Sclerosis Platform), K. Selmaj – neurologist, R. Nitsch – basic neuroscientist

• A. Background

Multiple sclerosis is a major, devastating neurological disease that affects individuals from adolescence to old age. It can present itself 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 the northern latitudes. The average prevalence in Europe is 50 to 200 cases per 100 000 inhabitants, and approximately 700 000 multiple sclerosis patients live in Europe today. The impact of multiple sclerosis on European healthcare systems is considerable. Patients develop neurological disabilities of various types and intensities, with 10 to 15% requiring a wheelchair or becoming bedridden. On the other hand, around 20% of patients maintain their professional and social activities for many years or even until the end of their lives. All multiple sclerosis patients require support from health and social programmes. In terms of its impact on the European economy, multiple sclerosis is among the most costly of diseases.¹

• B. Past achievements in Europe

In the last decade, the biggest achievement in multiple sclerosis research has been the development of new therapies that halt disease progression. The first therapeutic agent against multiple sclerosis, interferon beta, came from European laboratories. Important, basic immunological observations on the relationship between T cells and central nervous system (CNS) components, which have shed light on the underlying mechanisms of multiple sclerosis, have also come from European labs. The pan-European programme to screen the genome for multiple sclerosis-related genes (GAMES) is the biggest initiative of its type in the world so far.² Europeans have been responsible for the genetic profiling of multiple sclerosis brain lesions³ and for stem cell research in the context of repair in multiple sclerosis. Several fundamental observations made with magnetic resonance imaging (MRI) have helped to elucidate multiple sclerosis mechanisms.⁴ Clinical presentation of multiple sclerosis is heterogenic, suggesting that brain destruction is the result of multiple mechanisms, and at least four different patterns of demyelination have been identified in multiple sclerosis brains.⁵

• C. Proposal

Multiple sclerosis is a degenerative autoimmune disease of the CNS in which the myelin sheath of neuronal axons is gradually destroyed. Myelin-specific CD4+ Th1 cells (a type of T cell) are implicated in the processes that lead to that destruction. T cell activation and function, the molecular mechanisms of T cell receptor (TCR) co-stimulation and antigen presentation should therefore remain at the centre of multiple sclerosis research.

Further studies are required on the antigenic properties of myelin and other CNS components, as well as potential exogenous antigens. The discovery of new classes of antigens or neo-antigens derived from post-translational or metabolic modifications could shed new light on multiple sclerosis pathogenesis. Antigen-presenting cells such as dendritic cells, macrophages and microglia could significantly influence the aberrant induction of immune responses. A critical point in autoimmune processes is the insufficient downregulation of TCR, either due to continuous antigenic stimulation or to the influence of regulatory cell populations, so there is a need for studies on the generation and function of immunoregulatory cell populations. Recently, several new categories of immunoregulatory cells have been discovered. In the light of recent complications with non-specific immunoregulatory therapies, finer, antigen-specific forms of immunotherapy are now the subject of great interest. Although multiple sclerosis is associated with a Th1-type immune response, the role of antibodies in tissue destruction remains controversial and should be explored. Strategies that have been successful in the identification of pathogenic antibodies in other conditions might be of use here.

Recent studies in multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis (EAE), suggest that even during the early phase of inflammation, neuronal pathology contributes to disease severity. It is now clear that long-term disability in multiple sclerosis correlates more with axonal damage than with the degree of demyelination. Protection of neurons should therefore be explored as a possible therapeutic approach. Genetic studies have revealed that many genes contribute to multiple sclerosis. Whole genome screens have highlighted several regions of interest, and fine analysis of these regions as well as further association studies will reveal more about the genetic basis of the disease. New MRI techniques, advanced spectroscopy, functional studies and the combination of MRI with molecular testing should help to elucidate further the disease processes. And finally, more research is needed on potential repair strategies. Following the immune attack in multiple sclerosis, very limited repair takes place in the injured CNS tissue. The reasons for this are not known, but research into mechanisms controlling the regrowth of myelin, as well as the differentiation of oligodendrocytes from progenitor cells and their subsequent maturation, could be informative here, pointing the way to stem cell-based and other therapies for enhancing the repair of multiple sclerosis lesions.

- D. Significance of increased research

The last decades have brought considerable progress in multiple sclerosis therapy. For the first time, multiple sclerosis patients have been offered drugs that can halt the progression of their disease. However, the efficacy of these drugs is limited and on average only one third of patients respond well to them. For some forms of multiple sclerosis, such as primary progressive multiple sclerosis, there is currently no available therapy. Within five to 10 years, new drugs that influence the immune system more efficiently and selectively should be available. 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 multiple sclerosis patients.

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THEME 6: FROM BOVINE SPONGIFORM ENCEPHALOPATHY AND CREUTZFELDT-JAKOB DISEASE TO PRIONS AND NORMAL BRAIN PROTEIN HOMEOSTASIS

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- A. 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 1 to 2 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 to 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).¹ 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.

- B. 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.

- C. 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).^{2,3} 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^C) to the protease-resistant, pathogenic isoforms (PrP^{Sc}) requires the

addition of small quantities of PrP^{Sc}. 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^C to PrP^{Sc}. The cause of neurodegeneration in prion diseases is still unclear, however, and PrP^{Sc} may not be directly neurotoxic.⁴ 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.⁵ 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.

- D. 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^{Sc} isoform of the prion protein, or PrP^{Sc} 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 7: FROM HEAD TRAUMA TO THE BASIC MECHANISMS OF TRAUMATIC BRAIN DAMAGE

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- A. Background

Traumatic brain injury (TBI) constitutes a major health and socioeconomic problem.¹ 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.² The World Health Organization has projected that by the year 2020, road traffic accidents, a major cause of TBI, will rank third in 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 1000 people, the incidence being higher in Eastern Europe.

- B. 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. Intracranial pressure monitoring, which has now become a standard of care in more severe TBI patients, was introduced by French and Scandinavian groups. Measurements of cerebral blood flow, direct measurements of brain oxygenation and microdialysis for metabolic monitoring have also been introduced by European groups. Guidelines for the treatment of severe TBI were developed by the European Brain Injury Consortium (EBIC) and are currently recognised as an international standard.³ European groups have elucidated some complex pathophysiological mechanisms involved in TBI, research which has led to the development of various potential neuroprotective agents. Rehabilitation centres across Europe are focusing on early intensive rehabilitation, and very recently a disease-specific Quality of Life scale has been introduced by European investigators.

- C. Proposal

Intensive, multidisciplinary collaboration on traumatic brain injury 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 and develop appropriate prevention programmes. 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 be important for exploring the complex effects of injury on tissue perfusion, oxygenation and metabolism. An important focus in basic research is to explore possibilities for repair by promoting regeneration and exploiting brain plasticity. Europe currently has a distinct advantage over the USA in 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 traumatic brain injury is still in its infancy. Spreading cortical depression has been identified as one of the mechanisms with pathogenic potential in traumatic brain injury. Here, interdisciplinary 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), may serve as an example for multidisciplinary and multi-centre approaches to innovative research, and deserves encouragement.

The brain's response to injury may be genetically determined, and further research in the field of genomics and proteomics could shed light on individual variation in traumatic brain injury, and thereby guide the implementation of more individualised treatment. At the moment, the acute care management of traumatic brain injury 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 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 (contusions) within the brain. The benefits of performing an external decompression (removal of part of the skull) to treat raised intracranial pressure after traumatic brain injury are also controversial. Clinical trials are required to resolve these issues, but trials in traumatic brain injury remain a methodological challenge due to the heterogeneity of the disease.⁴ Ethical considerations are relevant here too, particularly in relation to decisions to intensify or withhold treatment, and to consent in 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.⁵

- D. Significance of increased research

A better understanding of traumatic brain injury and the development of new therapies will greatly reduce the suffering of both patients and their relatives, at the same time improving patients' quality of life and reducing the high personal and societal costs associated with traumatic brain injury.

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THEME 8: FROM BRAIN RECOVERY TO NEURAL PLASTICITY, GROWTH FACTORS AND OTHER BASIC MECHANISMS OF BRAIN REPAIR

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- A. Background

Information in the brain is stored in networks of interconnected neurons. These networks and supportive glial cells are formed during development and shaped in adulthood by neuronal plasticity, which is the basis for learning and memory. Plasticity is dependent on neuronal activity, which directs the formation and maintenance of active connections and the pruning of aberrant and inactive ones.¹ 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.^{2,3} Growth factors support neuronal survival and control neuronal connectivity during development and after trauma. The expression of these growth factors is increased by exercise and enriched environments, which can

also lead to enhanced recovery following brain injury.¹ 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.⁴ Systemic delivery of small molecules that stimulate neurogenesis or trophic factors is an attractive therapeutic approach for the pharmaceutical industry.

- B. 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.^{1–5} The application of gene and cell therapies with the aim of enhancing neuronal recovery has been pioneered and developed by European groups.^{2,3} and these approaches are now being followed up by small biotech companies in Europe (such as Stem Cells Sciences, Oxford Biomedica and Neuronova AB). 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.

- C. 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, middle cerebral artery occlusion, 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 which 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.

- D. 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 9: FROM BRAIN TUMOURS TO NORMAL MECHANISMS OF BRAIN CELL PROLIFERATION

M. Westphal – neurosurgeon, M Chatel – neurologist, M Dubois-Dalcq – basic neuroscientist, J Mossman – patient (cancer groups)

- A. Background

Approximately 30 000 Europeans 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 the less aggressive form of the disease have long survival, the prevalence of brain tumours in the European Union is around 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 have different tumour types because there are differences in their neural, glial and neuroglial progenitor cells. 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 systemically applied drugs. Almost no progress has been made in the treatment of glioblastoma, and average survival times have remained around 12 months for the past 60 years. The brain is considered a terminally differentiated organ with little cell proliferation or cell renewal, so any tumour can be considered a reappearance of a proliferative phenotype. Understanding proliferation and

differentiation of glial cells also has implications for improving brain repair after inflammation, stroke or injury.

- B. 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 well as a study demonstrating the importance of correlative genetics.^{3–5} 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.^{1–2} Europeans have also made major contributions to the biology of glial scarring and the inhibition of glial or neuronal cell motility by repellent molecules.⁴

- C. Proposal

Research into brain tumours must become more integrated with 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 (CNS). Glioma cells seem to escape that apoptotic mechanism. Two strategies for intervention are to try to reinstate that mechanism, or to use the migratory properties of the cells to attract them with appropriate attractants back to their origin, which is 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 glial or neuroglial stem cells, and how many normal stem cells are there in the adult brain?

(2) Mechanisms by which glial scarring occurs, without leading to 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.

(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 knock-outs 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, SCID mouse or nude rat backgrounds to allow for xenotransplants to be tested, as well as the recruitment of hematopoietic 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 a Europe-wide effort to build tissue arrays. A European Commission-funded (FP5) programme already exists for

sustained drug delivery to the brain by biodegradable polymers (Biodegradable Controlled Drug Delivery Systems for the Treatment of Brain Disease, coordinated by the University of Angers, France).

- D. Significance of increased research

Neurobiology and neuro-oncology are just beginning to be integrated, but in the US this has been accomplished in only a few academic centres. Europe is strong in both glial biology and neuro-oncology, but its expertise is 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 10: FROM EQUILIBRIUM- AND ATAXIC DISORDERS TO NETWORK OPERATIONS IN THE CEREBELLUM AND THE VESTIBULAR SYSTEM

NOT RECEIVED

THEME 11: FROM PERIPHERAL NEUROPATHY AND MUSCULAR DISEASE TO NORMAL FUNCTION AND GENETICS OF NERVE AND MUSCLE

T. Balta – patient, I. Illa – neurologist, U. Suter – basic neuroscientist

- A. 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.

- B. 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.¹ Trials of promising therapies such as exon skipping and stem cell transplantation are under development in European centres.² 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.³ Regarding neuropathies, European efforts have made possible the discovery of new genes and proteins, leading to a new classification of hereditary neuropathies.⁴ Progress has also been made in the study of ALS.⁵

- C. 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 co-stimulatory 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 neuroimaging, 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. Trans-European epidemiological studies and multidisciplinary training programmes should also be established.

- D. 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 side 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 render them effective and safe for the treatment of patients with neuromuscular diseases.

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THEME 12: FROM SPINAL CORD INJURY TO BASIC SPINAL CORD MECHANISMS

J. Schoenen – neurologist, G. Brook – neurobiologist, F. Scholtes – neurosurgeon, D. Martin – neurosurgeon, R. Franzen – neurobiologist, O. Kiehn – basic neuroscientist

• A. Background

Worldwide, around 100 000 people suffer traumatic spinal cord injury (SCI) each year. In 2005 the number of spinal cord-injured patients was estimated at 2.5 million people worldwide, over 500 000 of those being in Europe. About half of SCI are the result of traffic accidents, and more than half occur in the 16–30 age group, men being more frequently affected (80%) than women (20%).¹ 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.² Each year, €4 billion are spent in the management and care of SCI patients in Europe. This does not take into account the social costs of SCI: for example, the need to assist the affected individual in their everyday activities or to adapt their housing to accommodate a wheelchair.

• B. 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 time points and targets which are amenable to post-lesional intervention strategies:

(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).³

Many highly promising experimental intervention strategies 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, little if any clinical progress has been made in neuroprotective strategies.

• C. 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, for example, recruitment of inflammatory cells to the lesion site, expression of pro-inflammatory cytokines, release of prostaglandins, free radicals and cytotoxic molecules.⁴ Central to such research will be the clear identification of the duration of the clinical window of opportunity for the range of injury types.

The versatility of stem cells and progenitors has led to substantial interest in the use of such cells for transplant-mediated replacement strategies.⁵ Although embryonic stem cells have the widest potential 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 to both central and peripheral nervous systems will require further research. In addition, the development of high field magnetic resonance imaging (MRI) for clinical application will allow more detailed imaging of the lesion site as well as any spared tissue. 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. The development of more objective, computer-assisted analytical methods will be of substantial importance. There is no doubt that the combination of several intervention strategies will be necessary in experimental and clinical SCI to obtain clinically satisfactory functional recovery.

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. 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 treatments. 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.

• D. 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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6.4 REVEALING PAIN MECHANISMS AND THEIR CONTROL

Section editor: Jes Olesen (EFNS)

THEME 1: FROM MIGRAINE AND OTHER HEADACHES TO NEUROVASCULAR REGULATION AND BASIC MECHANISMS OF HEAD PAIN

A. Craven – patient (Migraine Association of Ireland), J Olesen – neurologist, A Parsons – industry (GSK), D Pietrobon – basic neuroscientist

• A. 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. The impact of tension-type headache, especially chronic tension-type headache, is much greater. Almost 20% of all absenteeism from work is caused by headache. It affects females more than males, mostly during their productive years. Headache affects quality of life much more than many diseases traditionally considered to be more serious. The estimated cost to the European economy of migraine alone exceeds €20 billion per year.

• B. 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.¹ Regarding migraine, they developed or discovered:

- Brain blood flow changes suggesting cortical spreading depression
- Pivotal messenger molecules such as calcitonin gene-related peptide (CGRP) and nitric oxide (NO)
- New therapeutic agents called 5-HT₁ agonists (triptans) and CGRP antagonists;²
- The first two migraine genes associated with a rare subform called familial hemiplegic migraine
- The first knock-in mouse with increased liability to spreading depression;³
- The neurobiology and imaging of pain pathways from perivascular nerve fibres in the head via brain stem to cortex.⁴ Regarding other headaches, they developed or discovered:

- (1) Pathophysiological mechanisms of tension-type headache
- (2) The impact of medication over-use on headache
- (3) Neuroimaging abnormalities in cluster headache and related syndromes.⁵

• C. 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 two already identified for familial hemiplegic migraine, affect ion channels or other mechanisms 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 anti-migraine 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 inhibition. 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 into environmental triggers and other aggravating factors. Very early mechanisms are best studied in experimentally provoked attacks, while spontaneous attacks reveal later changes. High field magnetic resonance imaging (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 and CGRP 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 understood. 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. Only a European wide research programme uniting all the best groups can ensure that Europe continues to dominate this field.

• D. Significance of increased research

The advent of new migraine drugs called triptans has greatly improved the acute treatment of that disorder. However, no new specific drugs have been developed 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 side effects could greatly reduce the enormous societal and personal costs of headache. More importantly, they could relieve the unbearable 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 2: FROM CHRONIC PAIN TO CENTRAL NERVOUS SYSTEM PAIN PROCESSING AND MECHANISMS REGULATING PERIPHERAL SENSORY NERVE TERMINALS

C. Belmonte – basic neuroscientist, G. Cruccu – neurologist

● A. Background

Chronic pain is often defined as pain which lasts for a prolonged period of six months or more. It has a detrimental effect on physical health, daily activity, psychological health, employment and economic status. People with chronic pain suffer on average for seven 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. For example, in the UK it was estimated that back pain led to 45 million days lost from work per year.¹ More than 40% of chronic pain sufferers say their pain has an impact on their everyday activities, from lifting and carrying to taking exercise and sleeping. 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.

● B. 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 elements, autonomic and motor responses, an emotional component and cognitive-evaluative aspects of the pain experience. The neurobiological basis of pain sensations was first established by European neuroanatomists and neurophysiologists such as Sherrington and von Frey at the beginning of the 20th century. More recently, at the peripheral level, Europeans defined the role of capsaicin as a specific activator of pain nerve fibres² and identified the existence of silent nociceptors, or the correlation between pain nerve fibre activity and the attributes of pain sensations in humans.³ 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,⁴ and to the identification of neurotransmitters and neuromodulators in pain excitatory and inhibitory pathways. They have also provided critical information about the molecular basis of nociception at all levels of the pain processing pathways.⁵

● C. Proposal

Researchers are working hard to identify and clone ion channel and receptor molecules involved in the transduction of physical and chemical stimuli by nociceptive and non-nociceptive primary sensory neurons. This type of study should be extended to the molecular and genetic identification of the ion channels and receptors that detect and encode noxious stimuli in nociceptive endings, paying particular attention to sodium channels and to the members of the TRP channel family, as well as to the molecular mechanisms of modulation of the transduction process during acute pain and when inflammation and injury are established (peripheral sensitisation). Knowledge about the molecular and cellular basis of neurogenic inflammation and the role of neuropeptides also needs to be increased. The genes and molecules that participate in peripheral pain transduction and signalling are targets for developing genetically modified animals and novel drugs that may help us to understand pain at the first step of the neural processing pathways. The use of recording techniques such as microneurography in humans may

help to correlate peripheral nerve activity with the attributes of the pain sensation.

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. The functional heterogeneity of spinal neurons, their synaptic connectivity, the nature of the neurotransmitters and receptors involved in spinal pain pathways and the functional properties of spinal circuits, as well as their inhibitory and excitatory modulation, should be studied intensively. Changes in the excitability and functional organisation of spinal pain pathways in developmental and pathological conditions needs to be explored further, combining molecular, immunocytochemical and electrophysiological approaches in intact and genetically modified animals during acute, chronic and neuropathic pain.

This type of study should be extended to pain-related regions and circuits at supraspinal levels of the central nervous system, with particular emphasis on the modulation of pain processing by opioids and the molecular, cellular and network substrates of tolerance and addiction. Areas in the forebrain involved in the sensory discriminative, cognitive and affective aspects of pain need to be identified with non-invasive imaging and recording techniques such as functional magnetic resonance imaging and magnetoencephalography in awake animals and humans. Reliable experimental models for studying osteoarticular and cancer pain should be developed, in which treatments can be tested. At all levels of the pain pathways the plasticity of synaptic connections and characteristics of transmission and receptor expression for the different neurotransmitters must be studied in chronic and neuropathic pain conditions, using whenever possible in vitro models such as cell cultures and tissue slices.

● D. Significance of increased research

A deeper knowledge of the molecular, cellular and integrative mechanisms involved in pain processing is urgently required if we are to identify specific targets for the treatment of chronic and neuropathic pain, as well as targets for more specific and safer analgesic drugs. This is the only way to help the millions of Europeans who suffer from chronic pain.

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6.5 REHABILITATION, PSYCHOSOCIAL CARE AND PREVENTION

Section editor: Mary Baker (EFNA)

THEME 1: IMPROVING LIFE FOR PEOPLE LIVING WITH BRAIN DISEASE: PSYCHOSOCIAL ASPECTS

M Barnes – neurologist, H Wittchen – basic neuroscientist, A Troostwijk – patient (Stroke Alliance for Europe), D Gauci – patient (GAMIAN Europe)

● A. Background

It is generally accepted that around 2 to 3% of the population has a severe disability, which is defined as needing the assistance of another person at least once every 24 hours. The

cause of disability in the majority of people who fall into that category is brain diseases, the most common of which are stroke, Parkinson's disease, multiple sclerosis, motor neurone disease and the after-effects of traumatic brain and spinal injuries. The overall prevalence of those diseases is around 2000 cases per 100 000 people.¹ Much of the research on common brain diseases has naturally been directed to the fundamental causes of the disease and/or to the alleviation of the impairments associated with it. However, an equally important component is the psychosocial problems that are associated with living with the disease. For example, research on multiple sclerosis indicates that most of the economic burden associated with the disease is related to the lack of employment opportunities for patients, rather than to short term healthcare costs.² The literature on traumatic brain injury clearly shows that psychosocial problems become more apparent when an individual is discharged from hospital and health and social services begin to withdraw.³ 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 the caring process.

- B. Past achievements in Europe

Much of the recent research on the psychosocial impact of brain diseases has been carried out in Europe. Studies on the psychosocial impact of traumatic brain injury were conducted in Scotland,³ while the study of the economic impact of multiple sclerosis was conducted in England.² European countries have only been partially successful in providing longer term community support for people with disabling brain disease, nevertheless Europe surpasses most of the rest of the world in this regard. Longer term psychosocial support is almost entirely lacking in many developing countries. Even many developed countries, such as the US, focus almost entirely on short term health 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 health and social structures 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.

- C. 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 that look at the epidemiology of specific symptoms. In the longer term it is mainly those symptoms that matter to the individual, rather than their diagnostic label. For example, we know the prevalence of incontinence problems for various specific diseases, but we do not know the prevalence of incontinence problems across the whole spectrum of brain diseases. We also have very limited knowledge of the prevalence of disabling spasticity in the context of motor disorders such as stroke and multiple sclerosis. Our knowledge of sexual dysfunction and relationship problems is particularly sparse.⁴ Simple, descriptive epidemiological studies of these disabling symptoms should therefore be regarded as a research priority. They in turn would enable a more coherent development of health and social support services.

Another priority for research should be the employment problems experienced by people with brain diseases.⁵ Many of

these diseases affect younger people who are still economically active, but our knowledge of the extent of physical and attitudinal barriers to their employment is very limited. A better understanding of these barriers, and their reduction or removal, could open up a broader range of employment opportunities for patients and lead to dramatic improvements in their quality of life. Similarly, our knowledge of barriers to people with brain diseases taking part in leisure and social activities is virtually non-existent on the European level, and research is needed in this area too.

- D. Significance of increased research

Many governments would argue, in some cases quite rightly, that there have been many improvements in terms of removing physical barriers to disabled people in recent years. For example, public transport systems are slowly becoming more accessible. 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 improving our basic knowledge of the barriers to employment, leisure and social integration experienced by people with disabling brain disease. It is only with a better understanding of those barriers that we will be able to devise ways to reduce them.

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THEME 2: IMPROVING LIFE FOR PEOPLE LIVING WITH BRAIN DISEASE: MEDICAL AND MEDICO-TECHNICAL POSSIBILITIES ENABLING PARTICIPATION IN LIFE

M Brainin – neurologist, M Nowotny – neurologist, A Butler – patient (European Disability Forum), M Graziano – patient (European Parkinson's Disease Association), B Zsolt – patient (GAMIAN Europe)

- A. Background

35% of the total burden of disease in Europe is accounted for by brain diseases, and 50% of years lived with disability are a direct consequence of brain diseases.¹ Due to the ageing of the European population, a further increase in disabling brain diseases can be expected. Rehabilitation, social inclusion and innovative strategies to promote participation in life by people with brain diseases have therefore become major concerns for the European community. The European Commission set out its priorities for mainstreaming the disability agenda across all areas of European Union policy in a recent communication.²

- B. Past achievements in Europe

Research in basic and clinical neuroscience 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 for

improving these patients' ability to function in their everyday lives, such as constraint-induced therapy. 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 for the severely disabled have been developed to reduce patients' dependency on carers, and even to enable communication.³ Neuroprostheses that work through functional electrical stimulation of the brain can improve motor function (eg grasping), autonomous function (eg micturition, continence, ejaculation) and sensory function (hearing, vision), enhancing an individual's independence.⁴ Other advances that have improved disabled patients' participation in life are the development of new languages for the blind and deaf, and the integration of these languages into information technology media. 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.⁵

- C. Proposal

Assistive technology plays an important role in enhancing participation where medicine can only provide 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, industrialists, users and policymakers will be necessary to make these innovations accessible to the disabled population. Mobility devices as common as wheelchairs still need improving, because while effective and user-friendly wheelchairs promote participation, ineffective ones represent a barrier to participation. Assistive devices for personal care, communication, sensory impairment, restoration of function and managing and coping with cognitive disorders need to be developed further, as has been stated at meetings of European experts. Environmental control systems and their switch devices 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 orientation and navigation aids for the visually impaired, communication aids for the aphasic community or text phones and other devices that enable deaf people to participate in telecommunication. 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. But overcoming disability goes beyond merely complementing the individual's deficits with assistive technology. It often requires a mix of mainstream and assistive technologies. Rapid changes in the mainstream technological environment can exclude disadvantaged populations from that environment, 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.

- D. Significance of increased research

Research on these issues will improve quality of life for disabled individuals who are experiencing barriers to participation in personal, social and civic life, enabling them to live fully, independently and according to their individual preferences and

needs. By encouraging equal opportunity, European society will benefit by seeing greater numbers of people participating in social affairs and in the workforce, and a reduction in the burden of care.

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THEME 3: FROM PHYSICAL, OCCUPATIONAL AND SPEECH REHABILITATION TO PLASTICITY OF THE MOTOR, COORDINATION AND SPEECH SYSTEMS

S. Cappa – neurologist, P. Videmsek – patient (GAMIAN Europe), B. Wilson – neuropsychologist

- A. Background

Motor and cognitive dysfunction after common neurological disorders such as stroke, traumatic brain injury (TBI) and neurodegenerative diseases represent an enormous burden of disability. About a quarter of stroke survivors are unable to walk, for example, while one third have persistent aphasia and 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 new research is opening up interesting perspectives on the association between drug therapy and rehabilitation. As a consequence, the development of effective non-pharmacological treatments aimed at the reduction of these disabilities would have a great impact on that burden.

- B. Past achievements in Europe

For many years, 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 has also been quite low, resulting in general uncertainty about the evidence-based efficacy of many non-pharmacological treatments. However, the situation is changing rapidly due to the increased interest of neuroscientists in recovery and rehabilitation.¹ It is becoming increasingly clear that any development in this field is likely to result from an increased 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. There is also an increasing awareness of the importance of collecting sound evidence about the efficacy of specific treatments.²

- C. Proposal

In the case of the rehabilitation of motor and cognitive disorders resulting from stroke, several promising lines of investigation are now open. 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 the 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 non-invasive cortical stimulation to maximise cortical plasticity and to increase the effectiveness of training interventions³ are in need of replication and extension. There is also increasing interest in the application of theoretically-driven approaches to rehabilitation practices, such as constraint-induced movement, language therapy and errorless learning procedures for the management of cognitive disorders. Other promising techniques include the use of electromyography feedback for motor rehabilitation and treadmill training for the treatment of walking disorders.⁴

Dementia is fast becoming one of Europe's health care priorities. Non-pharmacological treatments in this area are aimed at reducing the disability that is associated with progressive neurological dysfunction. There is some preliminary evidence that occupational therapy and cognitive rehabilitation may have a significant impact in this area, but further research is needed to clarify that. Another crucial area of investigation, which can be approached only within a multidisciplinary framework, is the combination of pharmacological treatments with training and rehabilitation. Pilot studies have been conducted in motor and language disorders, as well as in dementia, with promising results,⁵ but again these need to be replicated and extended.

- D. Significance of increased research

The potential impact of advances in non-pharmacological treatments on the burden of functional disability following common neurological disorders such as stroke and dementia is enormous. For example, any intervention which could significantly accelerate the time course of motor or language recovery in a substantial proportion of patients would have an impact on the length of in-patient treatment, on the potential to return home sooner and on the quality of life of long-term survivors of cerebrovascular disorders. Similarly, any limited 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 4: PREVENTION OF BRAIN DISEASES AND TRAUMA

Y. Lecrubier – psychiatrist, J-C. Corvol – neurologist, L. Forsgren – neurologist, A. Hagen – patient (Stroke Alliance For Europe)

- A. 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 and stroke 6 million. Their prevalence will substantially increase in coming years. Epilepsy affects 3.4 million people and Parkinson's disease more than one million.¹ 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, Parkinson's disease and epilepsy). Most start early in adolescence and their burden and cost are due both to the direct impact of the disease and to its more indirect effects on education and social skills learning.² Suicide is a behaviour 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 such diagnosis. The lethality of suicide attempts has been shown to be linearly correlated with the number of brain diseases both in the USA and in the EU.³

- B. 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 the identification of high risk or high cost groups is missing, which makes it difficult to make decisions about the allocation of resources. The evaluation and awareness 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.⁴ 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 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 sub-groups associated with different long term outcomes. Preliminary data suggest that for many brain diseases an early intervention is associated with modification of the course of the disease and/or a better outcome. Research on criteria and diagnostic tools that could improve the early identification of the disease are lacking for schizophrenia and Alzheimer's disease. Cohorts of patients identified and treated early versus 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 and the influence of psychosocial interactions and lifestyle affect the prevalence and outcome of brain diseases.

- C. Proposal

Large, multinational 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 Alzheimer's disease, schizophrenia and stroke). High and low prevalence brain diseases should be studied independently. Early identification of brain diseases or of major premorbid/prodromal features is currently one of the major challenges in many different brain diseases, especially where prevention of the disease or the effect 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 the early onset of 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 good or bad outcome. There should also be more research to improve recognition, treatment and pathway to care for brain disease patients, which will enable the role of primary care and psychosocial support systems to be assessed

and improved. Such studies could benefit from the diversity of health care systems and expertise available in the 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 health care strategies for preventing this rare but devastating event.

- D. 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 European Union population
- (2) Decreasing the prevalence and hence the cost of diseases that are currently responsible for about one third of total medical costs and even higher indirect costs due to loss of 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 response or treatment outcome will also be valuable for those working in other research areas such as neurobiology and genetics.

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THEME 5: ETHICS

A. Pessina – neurologist, T. Matthiessen – neurosurgeon, M. Leonardi – neurologist, A. Newton – patient (European Dystonia Federation), R. Elgie – patient (GAMIAN Europe)

- A. 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 re-defined,¹ 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.

- B. Past achievements in Europe

According to the Declaration of Helsinki² and the Oviedo Convention,³ in conducting medical research on human subjects, scientists should place considerations relating to the well-being 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 socially “weak” 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.

- C. 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 the need for 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.⁴ Even though animals have few rights of their own, they may not be used as mere 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 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 damage 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 misdemeanour, 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.

- D. 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 never to 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 to 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, pain therapy and the patient’s need for social integration, the quality of life of patients with brain disease will improve.

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6.6 SENSORY SYSTEMS AND AUTONOMIC DISTURBANCES

Section editor: Wolf Singer (FENS)

THEME 1: FROM HUMAN DISTURBANCES OF SMELL AND TASTE TO BRAIN MECHANISMS OF THESE SENSES

THEME 2: FROM BLINDNESS OR DAMAGED VISION TO BRAIN MECHANISMS OF VISION

THEME 3: FROM DEAFNESS TO BRAIN MECHANISMS OF HEARING

R Corradetti – basic neuroscientist, P Stoerig – basic neuroscientist, Eberhart Zrenner – ophthalmologist, D Koempf – neurologist, C Fasser – lay person (Retina International/Retina Suisse), L Findley – patient (European Parkinson's Disease Association), M Griffith – patient (Fighting Blindness), B Tenter – patient, M Bobeldijk – patient (European Federation of Hard of Hearing People)

• A. 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 handicap. Although rarer than other nervous system pathologies, sensory disturbances represent a substantial economic burden that is probably underestimated and often not taken into consideration in statistical assessments of health 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 over 85-year-olds in Europe, and approximately 10% of those aged between 75 and 84.¹ The incidence of these disorders is growing rapidly due to increasing life expectancy. Smell and taste disorders are common in the general population, 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 several neurological and psychiatric disorders, including Parkinson's disease, dystonia, autism and schizophrenia.

• B. Past achievements in Europe

Much of what is known about the sensory systems' anatomical and functional architecture was first described by European researchers. Ramón y Cajal discovered the basic structure of the cortex, Daniel and Whitteridge described the representation of the visual field in the primary visual cortex, and Zeki mapped the early extrastriate visual cortical areas. The investigation of cellular and genetic contributions to eye development has been supported cooperatively in Europe under the auspices of the research project EYE DEVELOPMENT. The 6th Framework Programme-funded project EVI-GENORET, which involves 23 groups in 12 countries, investigates the cell biology of the retina, its development and the consequences of genetic mutation, environmental factors and age. European research is at the forefront in this area, especially in elucidating the genes and pathophysiological processes involved, and the proteins expressed in the retina.

• C. Proposal

Increasing knowledge of the physiology of sensory systems will allow 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 five senses (sight, touch, hearing, smell and taste), and it is only very recently that the molecular basis of the mechanical sensations of touch and hearing was proposed.² 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. Investigation of animal models will continue to play a critical role in how we understand sensory pathway organisation and plasticity, from peripheral detection of sensory stimuli to their organisation into cortical maps and integration in behavioural adaptation to the environment. 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. We must continue to investigate the mechanisms of neurodegeneration, neuroplasticity and regeneration. Studies in animal models will help researchers to identify the role of genetic factors in establishing physiological functioning in each of the five sensory systems, as well as that of neurotrophic factors, neurotransmitters and neuromodulators. Novel ideas about neurochemical and neurotrophic factors that change synaptic morphology and function in sensory pathways need further development to clarify the adaptive changes produced by disease and to provide 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 guiding their re-integration into the appropriate sensory pathways. Stem cell implants are an example of such a therapy.³

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 of specific sensory cells.⁴ These therapies include genetic and stem cell approaches, as well as pharmacotherapy. 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. Drugs are already available that ameliorate the predictable, damaging effects of excessive noise and ototoxic drugs. The biggest 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. Genome-wide scans of large families with AMD should be performed to identify candidate genes and modulator genes. SNP association studies will elucidate the role of oxidative stress in the pathophysiology of AMD. The discovery of genetic mutations that affect vision and hearing (eg mutations in the gene coding for the sodium bicarbonate cotransporter NBC3⁵) will lead to a better understanding of basic processes of sensory function in general. New therapeutic approaches to AMD, such as the inhibition of neovascularisation (already in Phase II studies), could be applied to the treatment of other vascular diseases. Similarly, research on neuroprotection of retinal neurons will lead to the development of preventive measures. Electronic prostheses for the blind have shown beneficial effects and this research will be pursued further under European leadership.⁶

• D. 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. Vertical integration of basic science, genetics and clinical research is increasingly possible, but investment at each of these levels will be necessary. Further innovation in the therapy

of sensory disturbances will depend upon the efficient development of new medicines and therapeutic approaches on the basis of the neuroscience advances of the last decade, itself a major challenge. We need increased clinical trial capacity, reversing the long term trend toward fewer trials in Europe. It is now vital to foster clinical research for the identification and study of genetic, developmental and/or nutritional deficits and early life experiences that may influence vulnerability to sensory abnormality and disease. Turning biological small science into large scale research programmes is a supra-national project. A European approach is essential because expertise is widely distributed, and to ensure that large numbers of patients with relatively rare diseases are recruited to clinical trials.

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THEME 4: FROM BLADDER, SEXUAL AND OTHER DISTURBANCES TO FUNCTION AND BASIC ASPECTS OF THE AUTONOMOUS NERVOUS SYSTEM

C. Mathias – neurologist, D. Vodusek – neurologist, A. Taylor – patient (European Sexual Dysfunction Alliance), Baroness Masham of Ilton – patient (Spinal Injuries Association), C. Wayman – industry (Pfizer), R. Devereaux-Phillips – industry (Medtronic)

● A. 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 after 10 years, 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. 50% 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.

● B. 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 a leading

clinical textbook on autonomic failure.¹ Particular examples include advances in bladder and sexual dysfunction,² multiple system atrophy and orthostatic hypotension and syncope.³ Guidelines for investigation and treatment of autonomic disorders, established by European researchers, are used worldwide.^{4,5}

● C. Proposal

Major gaps exist in our knowledge of the epidemiology of autonomic disorders, and the problem these disorders represent for the European population is probably far greater than presently acknowledged. Little research has been carried out on the pathology, pathophysiology and aetiology of autonomic disorders, compared to other areas of neuroscience. For example, even normal brain control of basic functions such as micturition and blood pressure is not yet fully understood. Research on the pathophysiology of neurogenic autonomic dysfunctions from the molecular level to the system level will advance the possibilities of prevention and treatment. 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. Standardisation needs to be introduced into diagnostic testing. Both the health care community 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 needs to be mapped, especially that of its most common form, vasovagal syncope.

● D. 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). This has major significance for employment, driving, drug treatments and other considerations. Treating bladder and sexual dysfunction will considerably improve quality of life for those affected. Treating the former will reduce renal failure and attendant problems, for example in patients with spinal cord injuries. Interventions that rectify the primary deficit in many types of autonomic dysfunction are already a reality, so better identification of these conditions would lead to significant reductions in the burden of autonomic disorders. Research will also generate new drug therapies. Millions should benefit from a reduction in symptoms and a better quality of life.

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6.7 TOWARDS A BETTER DIAGNOSTIC AND THERAPEUTIC APPROACH: ENABLING TECHNOLOGIES

Section editor: Ian Ragan (consultant to Eli Lilly)

THEME 1: MOLECULAR IMAGING: FROM MAN AND ANIMALS TO MECHANISMS AT CELLULAR AND BIOCHEMICAL LEVELS

G. Knudsen – neurologist, D. Müller – basic neuroscientist, D. Nutt – psychiatrist, P. Warnke – neurosurgeon, A. Jensen – healthy volunteer, E. Rabiner – industry (GSK)

- A. 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 non-invasive 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.

- B. 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.¹ The correlation of molecular genetics with molecular and morphological brain imaging of tumours,² Parkinson's disease³ and depression has already yielded significant insights into basic pathophysiological processes and in the case of depression, the effects of treatment.⁴ However, while molecular imaging centres are well-established in the USA, similar centres are not yet as 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 FP5 Concerted Action, Neuroreceptor Imaging in Mild Cognitive Impairment, coordinated by Gitte Knudsen, and a Network of Excellence coordinated by Andreas Jacobs 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 field of molecular imaging is new and expanding rapidly, and it needs that long term investment if Europe is to become a leader in the field.

- C. Proposal

The first goal is the optimisation of technology for the integration of radiotracer, MRI and optical imaging methods. This requires the co-registration 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 which 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 non-invasive characterisation or phenotyping of animal models.

Molecular imaging will play an increasing 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 counter-images 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.⁵ 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 non-invasiveness 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.

- D. Significance of increased research

Intensifying research in molecular imaging will lead to new possibilities for: non-invasive 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 2: NEUROIMAGING: FROM CLINICAL APPLICATION TO BASIC PRINCIPLES

C. Ackerberg – patient, J. Masdeu – neurologist, R. Hari – basic neuroscientist, P. Magistretti – basic neuroscientist, H. Duffau – neurosurgeon, N. Ramsey – psychiatrist, C. Bunting – industry (Amersham)

- A. 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 and schizophrenia, begin long before they are clinically symptomatic.¹ Thus, ideal longitudinal markers should signal the pre-symptomatic stage, when therapies could be applied that

would stem or reverse the process of neuronal loss or other tissue damage that leads to symptoms. For many brain disorders, neuroimaging (including electrophysiological brain monitoring) meets the requirements of a such a biomarker.

- B. Past achievements in Europe

Most of the tools we use to image and monitor the nervous system were created in Europe. From Roentgen's seminal discovery at Würzburg (Nobel Prize, 1901), which allowed the application of x rays to visualise the skull, to the work of Peter Mansfield in Nottingham on nuclear magnetic resonance for imaging (Nobel Prize, 2003), Europeans have led the field in neuroimaging. The German Hans Berger recorded the human electroencephalogram (EEG) for the first time in 1924. Egas Moniz started brain angiography in Lisbon. In the past decade, the Trans European Network for Positron Emission Tomography laid the foundation for a solid and productive group of collaborative researchers in basic and clinical neurosciences. In functional imaging studies, statistical parametric mapping, born in London, is now used as a standard throughout the world.² Many other techniques, including voxel-based morphometry and dynamic causal modelling were also created in London. Three of the four leading manufacturers of neuroimaging equipment have their headquarters in Europe.

- C. Proposal

Development of more effective neuroimaging tools

Higher field magnetic resonance imaging (MRI), at upwards of 7 tesla (T), may permit the earlier diagnosis of brain diseases such as Alzheimer's disease by showing the loss of neurons of layer II of the entorhinal cortex,³ 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 foster the chemical diagnosis of a number of genetic disorders. Research on ways to improve 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.

Understand 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 disease.⁴

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 responsible for the disease. 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 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 progression is measured more reliably by neuroimaging than by other biological markers, allowing clinical trials to be completed with smaller patient samples in shorter periods of time. How the brain is reorganised after trauma, stroke or other injuries should be clarified and that knowledge used to devise better rehabilitation techniques.

- D. Significance of increased research

Along with genetics, neuroimaging will change the way medicine is practised, allowing for earlier diagnosis and more effective treatment of some of the most prevalent brain disorders, such as Alzheimer's disease, depression, schizophrenia, epilepsy and stroke. It also carries the promise of individualised medicine, so that harmful side effects can be prevented.

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THEME 3: GENOMICS AND PROTEOMICS: FROM APPLICATION IN BRAIN DISEASE TO BASIC SCIENCE

NOT RECEIVED

THEME 4: DRUG DELIVERY TO THE BRAIN: FROM HUMAN USE AND CLINICAL EXPERIMENTS TO CELLULAR MECHANISMS

J. Tonn – neurosurgeon, S. Froekjaer – neurologist and pharmacologist, J. Hubble – basic neuroscientist, M. Danhof – psychiatrist, B. Anders – industry (Lundbeck)

- A. Background

Brain tumours, neurodegenerative disease, stroke and head trauma lead to death or severe disability in a large number of patients all over Europe. Knowledge of molecular mechanisms and possible therapeutic targets for these conditions is steadily increasing, and many of these targets could be exploited, except that an effective means of delivering a therapeutic molecule to its target is often lacking. The intact blood-brain barrier (BBB) with its specialised micro-architecture, 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.

- B. 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.¹ 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.² Cells that have been genetically engineered

to produce and secrete bioactive molecules have been encapsulated into inert matrices which can be placed safely into the brain instead of directly implanting the cells.³ Another technology that circumvents the BBB is nanotechnology (liposomes, nanoparticles) that is designed to target specific areas of brain tissue via binding sites linked to the carrier surface which specifically interact with the targeted tissue.⁴ Intensive work has already been done in developing “intelligent liposomes” that are directed towards cerebral endothelial cells.⁵ Europeans have been at the leading edge of this research which, if it became more of a collaborative effort, could proceed much faster.

- C. 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 micro-environment 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 have to be developed in order to mimic conditions for delivering therapy.

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 used in 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 or neurodegenerative disease). With the help of imaging techniques such as diffusion tensor magnetic resonance imaging, a simulation can be developed to depict and monitor the distribution of the drug solvent. Computerised modelling of CED must be generated for exact pre-treatment planning of drug distribution. “True” molecular imaging (ligand specific positron emission tomography, for example) can be used to visualise targets and to help survey target-specific distribution of drugs. Carrier optimisation includes construction of carrier systems such as nanoparticles that have a surface specifically linked to ligands expressed on the surface of the target cells. Those target cells may be the affected cells themselves, or the microvascular system supplying 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 is crucial. In vivo experiments are needed to design antibody fragments that have a high selectivity and specificity, and that permeate the designated tissue after direct intraslesional application.

- D. 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 social 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 5: NEUROGENESIS, NEUROMODULATION AND NEUROSTIMULATION OF THE BRAIN

M Staal – neurosurgeon, T Meert – basic neuroscientist, P Bain – neurologist, K Mullett – industry (Medtronic), A Salomé – patient

- A. 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 or spinal cord 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. Electrical stimulation can be considered for the treatment of neurodegenerative diseases such as Alzheimer’s, Parkinson’s and Huntington’s diseases, as well as for multiple sclerosis, cerebral, coronary, and peripheral ischaemic conditions and hypo- and hyperkinetic movement disorders other than Parkinson’s disease. Other central nervous system diseases that are potentially eligible for electrical stimulation treatment are central and other forms of neuropathic pain,¹ headache, tinnitus, epilepsy and psychiatric disorders including obsessive compulsive disorder and severe major depression.² A pre-requisite for electrical stimulation 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 non-fatal, hence they place a heavy burden on the individual patient and on his or her family. Patients have a much reduced quality of life and are regular healthcare seekers.

- B. Past achievements in Europe

Neuromodulation by electrical stimulation has been a rapidly growing field for two decades. The first electrical stimulation targets, in the 1980s, were chronic benign neuropathic pain, ischaemic diseases (heart and extremities) and movement disorders, but electrical stimulation of the brain gained great acceptance after the first publication of the dramatic effects of chronic electrical stimulation of the subthalamic nucleus in Parkinson’s disease.³ Other targets were later identified for the treatment of movement disorders, and more recently psychiatric disorders, epilepsy and tinnitus.⁴ have been treated with electrical stimulation. In 1991 the International Neuromodulation Society (INS) was founded by a group of European medical specialists from different disciplines. The INS has grown into a worldwide, multidisciplinary organisation.⁵

- C. Proposal

There are many clinical and research centres across Europe which are focusing their activities on electrical stimulation treatment and exploration of new applications. 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 supranational cooperation of clinical and experimental efforts. 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 scattered throughout many different laboratories. New knowledge is not rapidly or efficiently exchanged yet. Ongoing clinical research into electrical stimulation 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 effect of electrical stimulation, the disorders which can be treated with it and the ideal patient profile, not to mention the optimal target for each disorder, side effects, the use of sophisticated peri-operative neurophysiological monitoring (micro-electrode recording) and the configuration of the stimulation parameters. Electrical stimulation 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 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 electrical stimulation remains limited. Therefore basic research should be a priority and integrated in 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 exchange of PhD students and creation of scholarships
- (4) finance implants in clinical studies for new applications
- (5) promote dedicated annual congresses for each application
- (6) make possible cost benefit studies
- (7) create a public information structure in close cooperation with patient organisations.

- D. Significance of increased research

Although electrical stimulation has shown tremendous therapeutic potential in a variety of pathological conditions, its place in the therapeutic armoury remains to be determined. Neurostimulation for some disorders has now gone beyond the experimental stage. Therefore research should be increased to determine the place and working mechanisms of electrical stimulation and its eventual competitive or synergistic role in relation to more classical, mainly pharmacological, approaches. At this stage the results of many clinical studies using electrical stimulation show a high degree of clinical efficacy and satisfaction among patients, as measured by improvement in quality of life. Cost-benefit analyses should be encouraged to demonstrate the benefits for the whole of society. Many of these patients withdraw from society, but after electrical stimulation treatment some of them are able to reintegrate into family and social life and even take up or resume work.

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THEME 6: NANOTECHNOLOGY: FROM BASIC SCIENCE TO BRAIN APPLICATIONS

P Matthews – neurologist, H Markram – basic neuroscientist

- A. Background

Advances in materials science and chemistry now allow fabrication of structures on the nanometre scale (1/1 000 000 of a millimetre)—the size of large molecules. Metal oxide-coated nanoparticles can be coated with a broad range of outer studding molecules, including proteins.¹ Carbon nanotubes can now be generated that have single walls, that can be cut to a limited range of dimensions and filled with both large and small molecules.² Self-assembling DNA structures can be generated that have various dynamic structures.³ Such specifically interacting but flexible structures can be linked with fluorescent markers to allow local signal detection by virtue, for example, of conformational changes in fluorescence energy transfer between attached moieties or, with potentially even lower detection limits, dye-enhanced Surface Enhanced Resonant Raman Spectroscopy (SERRS).⁴ These advances in basic technology have contributed to a new range of nanofunctionalities. Biosensors can be manufactured by linking nanostructures to specific interaction and reporter groups. Fluorescent nanostructures can make use of quantum dot technology—non-bleaching fluorescent semiconductors that can be tuned over a broad range of frequencies to allow simultaneous multidimensional reporting. Conformational changes arising from environmental changes (changes in pH or local oxygen concentration, for example) can be used to alter interactions and reporter responses. Nanostructures can also be used as basic delivery systems for large or small biomolecules. They can be used to store information as part of quantum computing networks or, in conjunction with polymers, integrated with tissues in micro-engineering applications.

- B. Past achievements in Europe

Significant achievements in nanotechnology have been made in Europe and are now developing in European laboratories. For example, the Bionanotechnology Interdisciplinary Research Centre, based at the University of Oxford, has provided a unique “centre without walls” that brings chemists, material scientists, physicists and biologists together to define nanotechnology approaches that can either interact with, or be informed by, biological systems behaviour. More European research is needed, however, with a drive towards specific applications.

- C. Proposal

The technology will be driven by greater expertise in materials science and physics at the nanoscale. However, for neuro-applications, additional knowledge is necessary—specifically, a better understanding of cell membrane conductance and signalling properties. Armed with a better definition of the highly efficient ways in which ionic charge transfers work in biological processes, researchers could develop improved interfaces between nanodevices and biological systems.

Quantum computing uses quantum states to store information. Because of the very low energy states involved, quantum computers could potentially interact closely with biological systems. Powerful computational devices could be linked directly

with the human nervous system, giving rise to “brain-building” via neural prostheses—though this remains a horizon technology for which long-term investment is needed.

A shorter term goal would be to develop highly informative molecular biosensors. Nanostructures could be used to encapsulate reporter molecules for the major non-invasive imaging tools of magnetic resonance imaging, fluorescence and positron emission tomography or single proton emission tomography. Responding to local state fluctuations driven by molecular events such as conformational changes, such sensors could be engineered to be sensitive to a broad range of phenomena both between and within individual cells. DNA-based structures potentially offer novel reporter technology based on gene expression and transcriptomics. Such structures could be transfected into cells and used to sample DNA-interacting molecules.

Nanoparticles are perhaps the most advanced of the potential biosensors because they are relatively easily synthesised. Core matrix materials can be engineered to include a broad range of encapsulated materials, such as materials conferring imaging contrast and movement in magnetic fields (eg iron oxide crystals), or substances with potential therapeutic effects. The coatings can be engineered with metal oxides to have a variety of optical absorption or binding properties. It is relatively easy to tag them with large molecules such as antibodies to target specific cell or tissue types. Of increasing interest is the notion of therapeutic delivery via locally interacting nanostructures that allow targeted, controlled release. Chemical signals or external low energy sources could be used to trigger that release—for example, by “tuning” a metal oxide coating to burst with microwave radiation.

This type of work has important, long-term therapeutic rewards, but remains for now basic and highly multidisciplinary. There is a need to establish programmes that link scientists interested in basic questions with those exploring neuroscience applications. Specific investment is needed in:

- (1) fundamental biophysics of charge transfer and membrane phenomena
- (2) understanding molecular properties on the nanoscale and particularly their unusual quantum behaviours
- (3) improving the selection of materials conferring particle functionalities
- (4) improving synthetic properties and control over the nano-engineering of those properties
- (5) development of imaging technologies based on coupling of nanostructures to sensor molecules and implementation of this in a biological context
- (6) investigation of systems level interactions of nanoparticles and their safety, with particular emphasis on immune responses and physical sequestration in the body.

- D. Significance of increased research

Miniaturisation of complex functional systems potentially allows minimally invasive reporting on cellular behaviour. Nanostructure delivery could pave the way for highly selective therapies. Nanoscale computational devices could “replace” neural structures after stroke and spinal cord injury, or even form the basis of neural “assist” devices for enhancement of the healthy brain. While the realisation of such possibilities is far in the future, the initial steps could be taken in the next five years, bringing with them high returns on forward-looking investment.

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THEME 7: BRAIN MECHANISMS AND APPLICATIONS OF BRAIN-MACHINE INTERFACES

N. Birbaumer – clinical neuroscientist, J. Millán – computer scientist, C. Neuper – psychologist, R. Douglas – basic neuroscientist

- A. Background

Brain-machine interfaces 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, brain machine interfaces 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.

- B. Past achievements in Europe

Europe plays a leading role in brain machine interface research, particularly for non-invasive brain machine interfaces for paralysed or locked-in patients^{1–3}, while the US is still dominating the invasive implantation of electrode grids in monkeys and basic invasive brain machine interface research.⁴ One US lab has received permission to implant 100 commercially developed micro-electrodes 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 non-invasive brain machine interfaces for locked-in patients with ALS. The website BCI 2000 (www.bci2000.org/BCI2000/bci2000.html), set up jointly by European and US researchers, allows access to programming guidelines for brain machine interfaces free of charge.² However, large scale clinical testing of invasive and non-invasive brain machine interfaces is lacking in both the US and Europe. Only a concerted, EU-wide effort from the best research groups can secure and increase Europe’s contribution to the brain machine interfaces field.

- C. Proposal

The theoretical and experimental separation of invasive and non-invasive human brain machine interface 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 non-invasive, commercially available and affordable brain machine interfaces that are tailored to specific applications. Brain machine interfaces 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 non-invasive brain machine interfaces, electrode grids for long-term scalp recordings are needed, along with amplifiers with DC 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 one square centimetre, 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 non-invasive brain machine interfaces 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 the non-invasive approach. The control offered by the brain machine interface should also be compared with that of devices that use autonomic changes 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 patients, should be trained to move their prosthetic devices or muscles directly via brain activity recorded through invasive or non-invasive electrode grids. Magnetoencephalography (MEG)—and electroencephalography (EEG)—brain machine interface 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 becoming much easier. Rehabilitation outcome and follow-up measures should include motor performance improvement in everyday life, but also cortical reorganisation induced by the brain machine interface training as measured by functional magnetic resonance imaging or positron emission tomography.

- D. Significance of increased research

After completion of the proposed research, the European consortium will offer specific brain machine interface 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 disabled access facilities in public places. The availability of such devices will also bring relief to patients, their families and societies 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 brain machine interface — for example, in early seizure detection and seizure control in intractable epilepsy.

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THEME 8: FROM NEURAL NETWORKS, OSCILLATIONS AND CODING TO NEURO-INFORMATICS

S Grillner – basic neuroscientist, D Willshaw – basic neuroscientist, M Lauritzen – neurologist, I Piper – neurosurgeon, C Godwin – industry (IBM)

- A. Background

To understand how the brain performs its many and complex integrated functions, and to use that knowledge for the treatment

and alleviation of disease, we need to understand all relevant levels of analysis from the molecular to the behavioural and cognitive, and to integrate our knowledge at all levels. This is a major challenge for neuroscience, because only in a few systems to date has it been possible to link the cellular and the behavioural levels. Due to the great number of dynamically interacting components in the brain, it is often impossible to gain fundamental insights into a function through experiments alone, and modelling is in most cases a necessary complementary methodology. Neuro-informatics is an emerging discipline with three major components: computational neuroscience (modelling), development of a federation of databases and development of information technology (IT) tools for analyses. Rapid advances in IT now allow the development of databases that extend from the molecular to the behavioural and clinical levels through all levels in between. Databases of this kind greatly facilitate the transfer of information from a clinical finding to structural biology, for example, or vice versa. Another important area is the utilisation of IT-based clinical data collection relating to brain diseases, and the possibility of discovering new and unexpected correlations through data mining. Models of disease become even more complex when they have to take into account the effects of medication on neural networks.

- B. Past achievements in Europe

Europeans have contributed significantly to the bridging of cellular and network levels and remain at the forefront of this field. Recent developments with regard to intrinsic function in the networks and microcircuits of the neocortex, hippocampus and motor system^{1–5} have provided important new insights. European researchers have also taken an active part in the development of neuro-informatics, with regard to both computational neuroscience and the development of databases. With American and Japanese researchers, in 2005 Europeans formed the International Neuroinformatics Coordinating Facility (INCF), which was initiated 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. It is likely that the secretariat of INCF will be located in Europe. It will be responsible for facilitating modelling and for coordinating informatics databases for neuroscience.

- C. Proposal

To understand the operation of the nervous system at the network level and ultimately in a global context, we need to comprehend the intrinsic function of the different functional modules of the brain. That means understanding the operation of cortical columns, micro-regions in the basal ganglia like striosomes and matrisomes, the micro-zones of the cerebellum and the neuronal networks that coordinate motor behaviour, among other 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 techniques. The latter will encompass biochemical modelling at the single cell level to 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 databases need to be designed. We envisage a situation in which specialists from many different disciplines, both basic and clinical, all design databases. These databases may eventually contain a great 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.

- D. Significance of increased research

No fundamental understanding of brain function can be gained from studying it at the cellular and molecular levels alone. We must also understand it at the network level. Until now, a correlation between a given gene, a transmitter 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 to achieve an understanding of the neural bases for that function or malfunction. Focusing on the microcircuit which serves as the interface between the molecular/cellular level and the systems/behavioural level is therefore of critical importance. The required multi-level approach will rely on a combination of different experimental techniques complemented by modelling approaches. This work will in turn be facilitated by the development of neuro-informatics databases.

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7.0 THE NEED FOR FUNDING

Neither at the European level nor at the national level is detailed information available about the funding of brain research. There are many reasons for this, the most important probably being that, in contrast to many other fields of biomedical research, brain research has implications beyond traditional health research. For example, understanding the functions of the normal brain has important implications for our educational systems, the IT industry and the design of marketing strategies, not to mention furthering our understanding and potential control of brain mechanisms underlying violence and addiction. Another reason is that, even within health research, distinctions are often made between psychiatric research, neurological research and neurosurgical research, leading to fragmentation of clinical research funding. Furthermore, basic research funding tends to be budgeted for separately.

To date, nobody has tried to analyse the funding of all these different branches of brain research simultaneously. The EBC together with the company Stockholm Health Economics is currently conducting a study to rectify this situation, work that is funded by a grant from the European Union. The results of the Resource Allocation for Brain Research in Europe (RABRE) project will be available in mid-2006. At that time, we shall therefore have reliable data on the allocation of resources to brain research in Europe, to measure against the cost of brain disorders as well as the demand for brain research whose applications may not be directly linked to the treatment of such disorders. It is already possible to conclude, however, that brain research is underfinanced with respect to the economic burden

represented by brain diseases alone. In its 2005 CDBE study, the EBC estimated the total cost of brain diseases in Europe to be €386 billion. Due to the scarcity of data in several of the countries included in that study, plus the fact that it restricted itself to the 12 most prevalent brain diseases, that was considered a conservative estimate. The true cost of brain diseases in Europe could be much higher, perhaps in the range of €500 to 700 billion. Pending the outcome of the RABRE survey, the EBC proposes that European funding for brain research should be increased to 0.13% of the annual cost of brain diseases, or €500 million per year.

Against the background of the European Union's stated goal to increase expenditure on R&D to 3% of the gross domestic product by 2010, the proposed increase in brain research funding is tiny, even taking into account that brain research funding is greater at the national level than at the European level.

Data on the financing of brain research at the European Commission level are available for FP5. In this programme, €85 million were spent on brain research, corresponding to 8% of the life science budget. This represents less than 0.01% of the annual cost of brain diseases for that period. Final figures are not yet available for FP6, but the indications are that at least 2–3 times as much will be spent on brain research under this programme as under FP5. Fortunately, this more positive attitude to brain research seems to be continuing in the European Commission's proposal for FP7, in which brain research has been designated a priority under the life sciences programme. What this will amount to in economic terms is not yet clear, and there are also obvious possibilities for funding brain research under FP7 outside the life sciences programme.

This consensus document describes 45 broad research themes, each of which should be suitable for one or more integrated projects and or strategic targeted research projects. It is the hope of the authors of this document and of the EBC's leadership that the document will help the European Commission to prepare a brain research programme under FP7. Furthermore, we envisage that this document may also have a considerable impact at the national level, by demonstrating to policymakers the important problems that could be elucidated or solved by more brain research, and by providing potential models for national brain research programmes. We also hope that it will help to promote coordination of national and Europe-wide research programmes. If that happens, European brain research will be greatly stimulated.

8.0 CONCLUDING REMARKS

The EBC has devised a three-step strategy to support brain research in Europe. Our first initiative was to calculate the burden and cost of brain disorders in Europe. Studies have revealed that brain disorders account for 35% of the total burden of diseases in Europe, and that they cost an enormous amount of money—approximately €400 billion per year. The second, ongoing initiative is the detailed analysis of the resource allocation to brain research in Europe, the RABRE project, whose results will be available in mid-2006. The third step is the present paper, whose aim is to show decision-makers as well as scientists and lay organisations what can be achieved if investment in brain research is increased.

The development of this consensus document demonstrates that a meaningful, comprehensive research programme can be developed in a bottom-up way by involving prominent researchers from clinical and basic science together with researchers from industry and patients. Clinical research organisations such as the European Federation of Neurological Societies, the European Association of Neurosurgical Societies and the European College of Neuropsychopharmacology have worked together with basic research organisations under the umbrella of the Federation of European

Neuroscience Societies to bridge the gap between basic and clinical research. Furthermore, the European Federation of Neurological Associations and the Global Alliance for Mental Illness Advocacy Networks have cooperated to represent the views of patients and citizens, ensuring that the proposed research programmes are acceptable to these groups.

The resulting document represents a huge step forward in formulating brain research programmes, providing a coherent and comprehensive picture of the possibilities for increasing investment in brain research in Europe. The very process of developing this document has brought many different research groups around Europe together. Thus, without any funding, the creation of the consensus document has initiated a potentially fruitful networking activity. The EBC hopes that participants will continue to elaborate on existing research networks after this document has been published, and that others will be inspired

through reading it to build new networks from scratch. In this way, several such networks will be ready to apply if and when calls are made by the EC for new brain research programmes to be funded under FP7. It must be pointed out that the groups that have produced the thematic papers are not necessarily the same groups that would apply for such a call. Those groups need to be much larger and new groups may be formed to successfully compete with those that have written the thematic papers. Free competition is of course an absolute requirement in science.

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