FORESIGHT STUDY:

Furthering Neuroscience Research on Neurodegenerative and Psychiatric Disorders

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CONTENTS

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INTRODUCTION

It is necessary to increase our knowledge of brain function and its disorders, develop more discriminating techniques and methodologies that will advance this aim, and find new therapeutic strategies for preventing, treating, or curing these intractable disorders, which represent a considerable social and economic burden in Europe, as elsewhere. Conversely, brain diseases are inestimable tools for approaching the mechanisms underlying normal brain function; the knowledge of the brain that is gained by studying these diseases is an important aim in itself. The more one knows about how the brain functions and how disease interferes with these functions, the more likely it is that effective therapeutic strategies will be discovered.

Data collected by the World Health Organization, in 2002, suggested that brain diseases are responsible for 35% of Europe's total disease burden, for a cost of 386 billion euros, a figure that reflects the medical, paramedical and social costs of these diseases which are a cause of severe handicap, often for many decades. This figure will grow because the European population is ageing, and the prevalence of the major degenerative diseases of the brain, Alzheimer's and Parkinson's disease, increases with age. It is instructive to compare the high cost of these diseases with the expenditures, in Europe, for research in neuroscience. The recent ERANET-NEURON survey, European Funding Programmes Neuroscience Research (Girgenrath and Dorlochter, 2008) found that only 20% of biomedical research spending was devoted to neuroscience. For the year 2006, a sum of only approximately 600 million euros was invested in neuroscience research by the European Commission and national and private funding agencies (compared to almost 4 billion by the American National Institutes of Health). Greater investment in research on brain disorders and their treatment would therefore be justified.

Two major categories of diseases affecting the brain disorders are the neurodegenerative diseases, such as the movement disorder Parkinson's disease and the cognitive disorder Alzheimer's disease, the underlying mechanisms of which have been under scrutiny for decades, and mental disorders, such as depression or schizophrenia, the biological substrates of which are still largely unknown. We have selected three neurodegenerative disorders (Parkinson's disease, Alzheimer's disease and multiple sclerosis) and three psychiatric disorders (depression, schizophrenia, and autism), which differ both in terms of their aetiology and their underlying physiopathology, to illustrate the problems encountered by research into these types of diseases and others (epilepsy, cerebrospinal degeneration, etc.), all of which are deserving of attention. In addition to their heuristic value, the six diseases that will be presented are, in themselves, largely responsible for the heavy burden of health care: Depression is both the most prevalent brain disorder (~150/1000 persons), and the most costly (~100 billion euros), followed by Alzheimer's disease (~70/1000 persons over age 65; ~55 billion euros), and Parkinson's disease (~10/1000 persons over age 60; ~10 billion euros). Schizophrenia (~100/1000 persons; ~6 billion euros), multiple sclerosis (1/1000 persons; ~9 billion euros) and autism (~/1000 persons; ~4 million euros) follow.[1] Except for Parkinson's disease and depression, which can be alleviated to some extent, there are no palliative

[1] Both care related and indirect costs are included. The figures were taken from *Wittchen HU, Jönsson B, Olesen J. (2005)* "Towards a better understanding of the size and burden and cost of brain disorders in Europe" *Eur Neuropsychopharmacol. Aug;15(4):355-6* -Collaboration to promote neurological research--the European Brain Council experience And *Olesen J., Baker MG, Freund T., Di Luca M, Mendlewiez J., Ragan I, Westphal M* (2006) "Consensus document on European brain research," *J. Neurol. Neurosurg. Psychiatry*, 77, i1-i49.

treatments for these or most other brain diseases, and no cures for any of them. Research into the causes and the pathophysiology of these diseases is therefore necessary to provide a scientific basis for the development of effective therapeutic measures.

In the next chapter, we will provide a brief description of these disorders that will allow us to pinpoint the problems that need to be addressed by future research, on these diseases. While some of these problems may be unique to one or another of the diseases, most are common to all. What research is needed and what is required to perform this research effectively will be discussed in the third chapter, irrespective of disease.

NEURODEGENERATIVE AND PSYCHATRIC DISORDERS:

PROBLEMS FOR RESEARCH

A. MODEL NEURODEGENERATIVE DISEASES

1. Parkinson's Disease

Parkinson's disease is an example of an adult-onset neurodegenerative disease (e.g., Alzheimer Disease, Amyotrophic Lateral Sclerosis, ...). It affects primarily one of the components of the brain's motor regulatory system, the dopaminergic neurons in the *substantia nigra*, a brain stem region, implicated in the initiation of movement. Loss of these neurons, and the resulting decrease in the neurotransmitter dopamine in the *striatum*, their target area, is responsible for the triad of symptoms characteristic of the disease, akinesia, rigidity and tremor, but other neuronal populations, using different neurotransmitters are affected as well, giving rise to a complex clinical picture that variably includes cognitive impairment, depression, sleep disorders, autonomic dysfunction.

The neuronal systems affected by Parkinson's disease and other parkinsonian syndromes are now quite well known, but why these specific neuronal populations degenerate is still not understood. In the vast majority of patients, no cause is known (sporadic Parkinson's disease). In a very few cases, toxins which affect mitochondrial energy production are known or suspected to be at cause, as in drug addicts intoxicated by a contaminant, 1-methyl, 4-phényl 1,2,3,6-tetrahydropyridine (MPTP), in their drug preparation, in farmers exposed to pesticides (e.g. rotenone, ...) , or populations, such as those in Guadeloupe, who regularly consume the tropical fruit soursop (corossol) containing the acetogenin annonacin. In ~10% of patients, mutations in single genes, more of which remain to be identified, cause the disease. Susceptibility genes are also being increasingly discovered. This clinical and etiological heterogeneity can be a hindrance to effective research on Parkinson's disease, since, when unidentified in the heterogeneous mass of patients with sporadic Parkinson's disease, it precludes the formation of the homogeneous cohorts necessary for clinical and biological research.

Neurotoxins, such as MPTP or rotenone, have become useful research tools, in particular to study the basic mechanisms regulating cell death and survival or the downstream consequences of dopaminergic neuronal death. However, mutant PD-causing genes (16 chromosomal regions and 13 different genes have already been identified) at present best allow investigation into the cellular mechanisms that underlie neuronal death in Parkinson's disease, and which in turn will lead to identification of scientifically validated targets for innovative treatments. The genes identified so far and the functions of the proteins they encode, which are extremely diverse, have given some clues as to the molecular dysfunction(s) that may lead to the death of dopaminergic neurons. Two of these are already widely investigated. The first is abnormal protein aggregation; the protein alpha-synuclein, encoded by the first Parkinson's disease gene to be discovered (*SNCA)* is also the major component of Lewy bodies, the histopathological hallmark of most forms of Parkinson's disease, suggesting the existence of a cell death mechanism that may be common to most cases, and which must be elucidated. The other important hypothesis to emerge from the genetic studies is mitochondrial dysfunction, in accordance with the above mentioned effects of mitochondrial toxins. At least 6 of the PD-causing genes (*parkin*, *PINK1*, *DJ-1*, *Omi/Htra2*, *SNCA*, *LRRK2*) have been associated with mitochondria. Their functions need to be explored. Mitochondrial dysfunction, and/or the cell death-inducing oxidative stress or metabolic deficiencies that result, are now

considered to be a potentially unifying hypothesis for the cause of dopaminergic neurodegeneration in Parkinson's disease, but what goes wrong and why is not clear. The identification of new causal genes, the elucidation of their functions and their possible implication in one or a few major molecular mechanisms leading to dopaminergic cell death will be one of the most fruitful avenues of research into Parkinson's and the most likely to identify new targets for therapy.

In addition to mitochondrial dysfunction, other potential pathogenic mechanism in Parkinson's disease merit further investigation. Among these, the possible role of a cellular immune response in the propagation of neuronal degeneration in Parkinson's disease is beginning to emerge. A very new hypothesis, the cell to cell (and perhaps from person to person) transmission of aggregates of mutant alpha-synuclein by a prion-like mechanism, is intriguing; this hypothetical mechanism, for which preliminary data exist, is potentially applicable to a number of neurological disorders where protein aggregates form (Alzheimer's disease and other tauopathies, Huntington's disease and other polyglutamine expansion disorders, ...). Also attracting attention is the association of glutatmate with dopamine in synaptic junctions and/or its possible neurotoxic effects due to defective interactions between the dopaminergic neurons and its neighbouring glial cells that regulate cellular and extracellular levels of this multifunctional aminoacid; glutamate has been suspected to play a role in several of the diseases that will be discussed below. Finally, search has begun for biomarkers of Parkinson's disease that can be visualized on brain scans or detected in body fluids (blood, urine, cerebrospinal fluid), ideally before clinical symptoms appear (60-80% of the dopaminergic neurons will already have been lost at this time), and can be used to monitor, quantitatively, the progression of the disease and the efficacy of therapeutic interventions agents.

Parkinson's disease is an exception among neurodegenerative diseases in that an effective symptomatic treatment exists since 1967: systemic administration of L-Dopa, the molecular precursor of dopamine that is converted to dopamine by the cells that have not yet died, and dopamine agonists, molecules that mimic the effect of dopamine on its receptors. L-dopa treatment, however, induces, with time, highly debilitating side-effects, such as fluctuations in efficacy and especially the irreversible induction of dyskinesias (violent involuntary twisting and turning), sleepiness, hallucinations, and behavioural disorders. Better dopamine substitutes or agents that act further downstream in the transmission process and innovative methods of administration (such as implantable pumps or diffusion capsules, vectors for transducing cells in the brain to reinforce expression of certain genes, native or genetically modified cells that secrete dopamine or appropriate growth hormones, ...), are therefore needed. Present research into the reprogramming of adult skin cells to into stem cells that can be differentiated into dopaminergic neurons (induced pluipotent stem cells (iPS cells), holds the promise of functional reconstruction of the damaged nigrostriatal dopaminergic neuronal pathway with autografts of such cells, if the problems surrounding how to place them in the brain and how to protect them from attack by the disease process are resolved.

Techniques for the reversible stimulation of specific territories of the brain motor system with surgically implanted electrodes has been very effective in a growing number of patients, especially younger patients with severely disabling dyskinesias. However, if the effective site of stimulation is now well-defined, how electrical stimulation actually works has not yet been clearly elucidated, and remains an important area of research, both for treatment as well as for understanding of the function of neural networks in the regulation of movement. Furthermore, the technique has potential for the treatment of other brain disorders. However, although well tolerated, implantation of the electrodes involves major brain surgery, brain imaging and electrophysiological recording, and a phase of testing to confirm the effective target. Less invasive methods, such as transcranial magnetic stimulation, are being explored, and this needs to be encouraged.

There is as yet no form of therapy that arrests the progression of Parkinson's Disease. For such agents to be discovered, progress is needed in our understanding of the molecular mechanisms underlying cell death and survival, in particular in dopaminergic neurons, and in the specific cellular pathways that are disrupted by the different causes of Parkinson's diseases, so that counter measures can be devised, and employed as early as possible in the course of the disease. The identification of biomarkers to detect the disease in its preclinical stage is therefore urgent.

The problems encountered in understanding and treating patients with Parkinson's disease, also apply to Amyotrophic Lateral Sclerosis. In this disorder, the specific populations of neurons that degenerate are the cortical and spinal motoneurons that stimulate muscle activity, leading to muscle atrophy and total paralysis including of respiratory function, and rapid death. A more systemic disease is suspected by some. Cognition is generally not affected, except in cases which are associated with a form of frontotemporal dementia. Although not as frequent as Parkinson's Diseases (0.5/1000 persons), it is even more handicapping. As in Parkinson's Disease, ~10% of patients have genetically determined forms of the disease that can now orient research. Approximately 20% of these patients have a mutation in the copper/zinc superoxide dismutase (SOD1), an enzyme implicated in the scavenging of ions that can cause oxidative stress, a potential cause of cell death, as suggested also for Parkinson's disease. The other genes that have been found mutated encode DNA/RNA binding proteins (TDP-43 FUS/TLS), suggesting that they play important regulatory roles in the motoneurons. Mutated SOD1 and TDP-43 form aggregates in cells, however, and proliferating immune cells have been observed, two points in common with Parkinson's disease. Very recently, a mutant gene known to cause spastic paraplegia (SPG11) another motor neuron disorder with cerebrospinal degeneration, was recently discovered in patients with autosomal recessive Amyotrophic Lateral Sclerosis, linking these previously distinct diseases. But the reason for the specific death of motoneurons in the patients and the molecular mechanisms by which this occurs are still unknown. With the exception of the glutamate release inhibitor riluzole that slightly retards the onset of respiratory failure, there is no treatment at all for this rare but most devastating disease. Brain-computer interfaces that would facilitate communication with patients would improve their existence, but would not change the outcome of the disease.

2. Alzheimer's Disease

Alzheimer's disease, the most frequent neurodegenerative disorder, is also the most frequent form of dementia, a category which includes the fronto-temporal dementias, dementia with Lewy bodies, and parkinsonian disorders, all of which need further research. The symptoms of Alzheimer's disease result from loss of neurons in the hippocampus and frontal cortex, which use acetylcholine as their neurotransmitter, and which are critical, not for movement, but for attention, memory, learning, and higher cognitive abilities. The earliest symptoms include forgetfulness, disorientation to time or place, difficulties with concentration, calculation, language and judgment. Neuropsychological testing has provided a detailed picture of the cognitive functions that are disrupted in Alzheimer disease, compared to other forms of dementia. Alzheimer disease has a long course and, as it progresses, some patients develop severe behavioural disturbances and may become psychotic, which is particularly difficult for caregivers. In the final stages, the affected individual is incapable of self-care and becomes bedridden.

The clinical diagnosis of AD is based on the results of neuropsychological tests and brain imaging showing atrophy of the hippocampus, but final confirmation of the diagnosis requires post mortem detection of the classical stigmata of the disease: fibrillary aggregates of abnormally phosphorylated forms of the protein tau in neurons and senile plaques containing an abnormal fragment of the amyloid precursor protein (APP) known as Aβ42, or beta-amyloid, surrounding

nerve terminals, and which is thought to cause synaptic dysfunction followed by neuronal degeneration. This peptide can also be quantified in cerebrospinal fluid, which makes it a possible biomarker for preclinical stages of the disease as well as for the consequences of therapies aimed at eliminating the abnormal protein. However, further analysis of the lesions themselves using the tools made recently available by proteic, proteomic and lipidomic approaches is necessary to understand why they form and how perhaps to prevent their formation and their toxicity.

The cause of Alzheimer's disease is unknown. The convergence of risk factors, which include advancing age, lipoprotein E epsilon 4 genotype, obesity, insulin resistance, dyslipidemia, hypertension, and inflammatory markers, as well as environmental factors, may play a role. Vascular disease, high blood pressure and high cholesterol levels in middle age appear to increase the risk of going on to develop AD in later life, a hypothesis that needs more attention. However, mutations in the genes encoding the amyloid precursor protein and in the presenilins 1 and 2 implicated in the processing of this protein can cause early-onset Alzheimer's disease (before the age of 65). Although they are responsible for less than a few percent of all cases, they clearly point to the toxicity of the beta-amyloid aggregates in senile plaques. Why these plaques form in the vast majority of patients without known mutations, and how to prevent this, is therefore the crucial question. The hypothesis of a prion-like mechanism for the propagation of the disease within populations of neurons has been evoked. Susceptibility genes have also been identified, suggesting that, in addition to beta-amyloid, faulty protein chaperone functions, abnormal lipid metabolism or chronic inflammation may also play a role. Abnormal mitochondrial dynamics have also been reported. In spite of the amount of research that has been dedicated to Alzheimer's disease, and the identification of major pathogenic elements, the mechanism underlying neurodegeneration in this disease has still not been elucidated.

Since the loss of a single category of neurons is responsible for the major cognitive deficits in patients with Alzheimer's disease, neurotransmitter replacement therapy, such as used to treat patients with Parkinson's disease, was expected to effective, but this has not proven to be the case. The use of cholinesterase inhibitors which prevent the degradation of acetylcholine in synapses have been reported to temporarily slow cognitive decline, but the results of these studies are not considered conclusive. Destruction of cholinergic synapses by the senile plaques may be one reason for this failure. The use of transcranial magnetic stimulation to enhance synaptic activity is being considered. However, without arresting the progressive neurodegeneration that underlies the symptoms of the disease, only temporary improvement can be expected. An attempt to stop neurodegeneration by stimulating an immune response against beta-amyloid, which was somewhat successful in a mouse model of Alzheimer disease, was not successful when tested in humans in that it caused meningo-encephalitis in 6% of the patients. This may be due to problems with the treatment protocol, however, rather than with the strategy itself, which is promising and merits continued efforts; other strategies to stimulate the degradation of beta-amyloid preventing its accumulation are also under consideration. All of these strategies are potentially applicable to other brain diseases (Parkinson's disease, ALS, the rare glutamine repeat disorders, ...) involving the accumulation of toxic proteins which is, however, often intracellular.

3. Multiple Sclerosis

Multiple sclerosis is the second cause of handicap in the young. Except for the few cases caused by gene mutations, multiple sclerosis is an autoimmune disease in which neural degeneration is secondary to an attack by the immune system against the myelin sheath, a cellular insulation surrounding certain nerve fibbers that increases the speed of the electrical impulses carried by the fibbers; it constitutes the so-called white matter of the brain. However, primary

neurodegeneration independent of the inflammatory attack, or chronic neurodegeneration due to low level inflammation, are now considered possible. The disease may be progressive or follow an early course of relapse and remittance followed by progressive aggravation. Depending on where in the brain the immune attacks occur, patients develop neurological disabilities of various type: numbness, fatigue, blurred vision, and clumsiness, slurred speech, weakness, loss of coordination, pain, uncontrollable tremors, loss of bladder control, memory and other cognitive deficits, depression, and paralysis. Muscle spasticity can affect balance and coordination, causing stiffness and involuntary jerking movement and, if untreated, can create contractures, or the "freezing" of a joint that prevents movement. Although some patients experience little disability during their lifetime, up to 60% are no longer fully ambulatory 20 years after onset; 10 to 15% require a wheelchair or become bedridden, and in rare cases the disease is sufficiently malignant to result in death.

The component of myelin that elicits the immune response remains unknown, and until it is identified, it will be extremely difficult to understand the pathogenesis of the disease. Wherever myelin is destroyed, a damaged area of white matter known as lesion or plaque forms. Over time, scar tissue develops at the lesion sites disrupting transmission of nerve signals, and preventing axon regrowth. The plaques can be observed by magnetic resonance imaging in white matter, notably in the brain stem, optic nerves, or spinal cord. In typical cases, the lesions tend to occur in periventricular areas and may occur in the *corpus callosum* consisting of myelinated nerve fibers connecting the two hemispheres of the brain. How to restore axon regrowth and effective myelination is the major challenge for research on multiple sclerosis.

Despite intensive efforts, the cause of multiple sclerosis remains unknown. Important efforts are needed to identify the myelin antigen that is attacked and to determine why the immune systems does not recognize it as "self." Several viruses and bacteria have been or are being studied to determine if they may trigger the disease but none have been proven to do so as yet. A deficiency in vitamin D, which plays a role in the immune system, has also been hypothesized. Interestingly, more females than males have multiple sclerosis, especially when onset is before age 15 years or after age 50 years, and males have a greater tendency to develop primary progressive disease, whereas females tend to experience more relapses, suggesting that a hormonal component affects the disease process, and needs to be elucidated.

Epidemiological data also shows that multiple sclerosis is as much more prevalent in temperate zones, than in the tropics, and Caucasians are more susceptible than other races (it is relatively rare among Asians). Immigrants, however, retain the same risk as in their countries of origin, suggest that early exposure to some environmental factor may predispose to the disease. Familial aggregation of multiple sclerosis is suggestive of a genetic predisposition to the disease, but this is difficult to distinguish from an environmental cause. Genetic studies indicate that the risk of multiple sclerosis may be associated with a cumulative effect of a number of genes, which in themselves have only small effects. The major histocompatibility complex (MHC) region on chromosome 6p21 harbours susceptibility genes as well as genes that might protect against the disease. Other genetic sequence variants associated with multiple sclerosis have also been identified. Much more research into the genetic and environmental susceptibility will be necessary to unravel the genetic and environmental factors predisposing to multiple sclerosis, an essential but difficult process.

Anti-inflammatory corticosteroid therapy is most commonly used for relapse management, as is the immunomodulator beta-interferons (1a and 1b). Glatiramer acetate, that mimics the peptide sequence of myelin basic protein, one of the components of myelin, is reported to decrease the

number and severity of relapses, slow the progression of the disease, and reduce accumulation of new lesions, but this is contested. Mitoxantrone (a DNA intercalator that affects lymphocyte proliferation, and natalizumab (a monoclonal antibody against the adhesion molecule VLA-4 that prevents migration of immune cells to the CNS) are also reported to be effective. The efficacy of these agents still needs confirmation and how these agents prevent relapses is still unknown, and immune therapies have serious adverse side-effects. No treatments exist for the primary progressive forms of the disease.

B. MODEL PSYCHIATRIC DISORDERS

1. Major Depression

Major or unipolar depression is the most frequent and costly of brain diseases. Certain neurological disorders, such as Parkinson's disease and multiple sclerosis can also involve depression, and some pharmacological agents, reserpine or beta-blockers, as well as substances of abuse appear to increase risk of the disease. Patients experience feelings of sadness, hopelessness, pessimism, loss of interest or pleasure in normally enjoyable activities. The probability of suicide attempts is high. Reduced self-esteem as well as emotional well-being in general is commonly observed. Patients may have cognitive disturbances, such as memory impairment, which have not yet been sufficiently documented in this disorder. In rare severe cases, motor disturbances and catatonic symptoms can be observed. Hospitalization may be necessary where there is self-neglect or a significant risk of harm to self or others. The course of the disorder varies widely, from a single episode lasting a few months to, most frequently, a lifelong disorder with recurrent major depressive episodes. The disease can worsen or develop into bipolar disorder with phases of mania and/or signs of schizophrenia that can lead to a psychosis. Tools for early diagnosis that would help prevent an unfavorable evolution of the disease are lacking.

As with most mental disorders, major depression appears to be multifactorial in origin: biological, psychological, psychosocial stressors, or a combination of these all play a role to varying degrees. It is generally admitted that depression results when a pre-existing vulnerability is activated by stressful life events. Vulnerability factors include low self-esteem and self-defeating or distorted thinking, significant losses in early life, trauma, childhood abuse, health problems, changes in social relationships, a death, adverse conditions at work, unemployment, poverty and social isolation. The heritability of major depression is estimated at 40%. The search for susceptibility genes is therefore essential. The serotonin transporter (5-HTT) gene has been reported to be a susceptibility factor, but this is still controversial, and no genetic causes of major depression have as yet been identified. How genetic predisposition and environmental factors interact in depression is still unexplained. Identification of the environmental (social) factors, however, would be a major advance in the prevention of the disease.

There is some evidence associating depression with smaller hippocampal volumes and loss of hippocampal neurons have been reported, correlated with memory impairment. This brain structure is also implicated in Alzheimer's disease and schizophrenia. An abnormality in a cortical brain area implicated in the modulation of emotional behaviour has also been reported. This structural effect is supported by evidence that levels of the neuronal growth factor BDNF, involved in neurogenesis, is drastically reduced in blood, and in the hippocampus and prefrontal cortex of depressed patients, and a common polymorphism in the BDNF gene has been related to reduced size and dysfunction of the hippocampus. Structural changes and neuronal loss have been also found in the amygdala and the ventral striatum, brain regions involved in the regulation of affective and negative emotion. A problem with corticosteroid regulation of BDNF may be implicated. It is imperative to elucidate the neurobiological mechanisms underlying the different behavioural disorders observed in patients. Investigations into the neurobiology of major depression have traditionally focused on the monoamine neurotransmitter serotonin as a key mediator and also on norepinephrine, since various antidepressant drugs are thought to work by increasing their levels in the synaptic cleft, but this hypothesis is controversial. Disturbances of the hypothalamic-pituitary-adrenal axis (HPA) have been described in depressed patients, but its role in depression needs further investigation.

There is no cure for major depression, but a range of antidepressant drugs appear able to correct the abnormal signals that control mood and thoughts. Their mechanisms of action are not understood. Most antidepressants work by increasing the levels of serotonin and norepinephrine in the brain, but an intact monoamine, and especially serotoninergic, system is necessary for therapeutic efficacy. These treatments also have important side-effects. Glutamatergic drugs also have slight antidepressant effects. A new type of antidepressant, an agonist of melatonin receptors that appears to improve quality of sleep, reported to be as effective as existing antidepressants, but without the monoamine-associated side-effects, should soon be available. Growth factor-based treatments to prevent or repair brain deficits in depression may also be promising. Non-pharmacological means, such as cognitive behavioural therapy, are also used to manage depression. At the other end of the treatment spectrum, electroconvulsive therapy has been used for drug-resistant severe major depression or in emergencies, such as catatonic depression when a patient has stopped eating and drinking or is severely suicidal. Other less drastic techniques of neurostimulation are now being tested, such as electrical stimulation of the vagus nerve, transcranial magnetic stimulation of the prefrontal cortex, and deep brain stimulation appear to have some effect; their study should be encouraged. The difficulty faced by therapeutic trials in depression is the lack of quantifiable biological markers of their effect.

2. Schizophrenia

Schizophrenia is a mental disorder characterized by abnormalities in the perception or expression of reality. Impaired reward processing, and failure of motivation are described. It is suspected to be a genetically based neurodevelopmental disorder, which may be exacerbated by environmental factors. There may also be a neurodegenerative component to this pathology, but this has not yet been insufficiently studied. Onset typically occurs between the ages of 15 to 25 years. Schizophrenia is often described in terms of positive symptoms (delusions, auditory hallucinations, and thought disorder, typically regarded as manifestations of psychosis) and negative symptoms or deficits (flat or blunted affect and emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation, which can be accompanied by depression, anxiety or substance abuse, leading to problems of social insertion and decreased longevity due to health problems or suicide. The manifestation of symptoms is quite diverse and may be difficult to distinguish from other psychoses. Improved criteria for early diagnosis are needed.

Environmental factors such as traumatic prenatal physiological or psychological events (viral infections, famine, war, intense stress..), an urban environment, social disadvantages(poverty, migration, racial discrimination, ...), childhood abuse or trauma have also been reported to be risk factors for the expression of schizophrenia in later life. However, genetic and epigenetic factors also may be involved. Rare chromosomal deletions and duplications have been found in 3% of patients. The COMT (Catechol-O-Methyl Transferase) gene, encoding an enzyme that degrades catecholamine such as dopamine, and the KCNH2 gene, which encodes a potassium channel implicated in the electrical activity of nerve cells, as well as abnormalities of other genes often involved in neuronal signalling and brain development, have been associated with schizophrenia, although these data need further confirmation.

The volume of grey matter in the brain especially in the prefrontal cortex, is reported to be decreased in patients with schizophrenia, in relation the duration of psychosis. There is debate, however, as to whether neurodegeneration in schizophrenia begins at the time of symptom onset or earlier, or whether it is a neurodevelopmental process that produces abnormal brain volumes at an early age. Brain activity appears to be altered in patients, particularly in the frontal cortex implicated in adaptive behaviour and in the hippocampus and temporal cortex implicated in

memory and other cognitive functions, which are also altered in patients with dementia. Increased dopamine release by the mesolimbic dopaminergic neurons, implicated in emotional regulation, and decreased release of glutamate, the major transmitter in cortical neurons, may underlie the symptomatology of schizophrenia, but the cause of these anomalies and the mechanisms which underlie them are still unknown. Research into the biological substrates of schizophrenia is much needed.

Glutamatergic drugs are already in clinical trials in schizophrenic patients, and antipsychotic drugs which decrease dopamine activity in the mesolimbic pathway of the brain are effective in controlling the positive symptoms of the disease. However, they also decrease dopaminergic transmission by the nigrostriatal neurons leading to parkinsonism and the risk of developing irreversible dyskinesias (neuroleptic malignant syndrome), a rare potentially fatal neurological disorder. Drugs that have less of these side effects have anti-serotoninergic activity, possibly leading to depression or other debilitating side effects. Cholinergic therapy might also be envisaged for the cognitive problems in patients with schizophrenia, although they have not been notably successful in Alzheimer's disease, and lithium treatment might help by stabilizing mood. None of the antipsychotic drugs significantly ameliorate the negative symptoms of schizophrenia.

In the absence of treatments that effectively address the underlying biological dysfunctions in patients with schizophrenia, different forms of psychotherapy (cognitive behavioural therapy, cognitive remediation, cognitive enhancement therapy, family therapy, ...) are being developed to help to cope with the cognitive and behavioural disorders in patients. Electroconvulsive therapy may be prescribed in cases where other treatments have failed, especially where catatonia is present. As with other forms of electrical stimulation, the mechanism by which this treatment works is not known. Newer forms of electrical or magnetic brain stimulation may have positive effects, particularly against hallucinations, without the risks associated with electroconvulsive therapy; research on these procedures, and other procedures that would stimulate brain plasticity, should be actively pursued. Given the developmental origin of this disorder, an early diagnosis that would permit intervening therapeutically at an age when neural circuits are still plastic would be of great interest. The biological markers that would help make an early diagnosis are lacking. Identification of factors that would stimulate hippocampal neurogenesis, or growth factors that would prevent neurodegeneration or developmental abnormalities should be stimulated.

3. Autism

Autism, the most severe of a group of neurodevelopmental conditions referred to as Autism Spectrum Disorder (ASD), is a developmental disorder of the brain that prevents organizing and understanding information transmitted by the senses. It is characterized by a triad of deficits: disturbed social behaviour, atypical verbal and nonverbal communication restricted interests and activities, which can be accompanied by repetitive behaviours. Sleep problems, epilepsy, anxiety, obsessive-compulsive disorder, aggressivity, mental retardation and metabolic defects, such as phenylketonuria, are common. Superior perception and attention or unusual responses to sensory stimuli can also be observed, and an estimated 0.5% to 10% of individuals with ASD show unusual abilities, such as a capacity to memorize trivia, but also the prodigious talents of autistic "savants". Attention deficit hyperactivity syndrome or Gilles de la Tourette syndrome are often present as well. Some risk factors, such as advanced maternal and paternal age, have been reported to be associated with this disease, as well as obstetric conditions that include low birth weight, duration of gestation and hypoxia during childbirth. Environmental factors, such as teratogens that have been related to the risk of autism, appear to act during the first eight weeks after conception, suggesting that autism arises very early in development.

A genetic susceptibility to this disease is now considered probable; heritability has been estimated at 90%, although it cannot be explained by known genetic factors. The recurrence rate in siblings of affected children is 2% to 8%, which is much higher than the prevalence rate in the general population but much lower than in diseases linked to mutations in a single gene, indicating that autism is not a Mendelian disorder, but rather linked to a combination of genetic factors. Large chromosomal abnormalities (3%-7% of patients), including the most frequently observed maternal 15q11-13 duplications (1%-3% of patients) are observed, and genetic susceptibility loci (2q24-2q31, 7q, and 17q11-17q21) and autism-associated genes implicated in synaptic function (*NRXN1, NLGN3 and NLGN4, SHANK3, and CNTNAP2*) have been identified in a few cases. It should also be possible to use animal models to map genes or loci involved in individual behavioural traits that are characteristic of schizophrenia, then to test these genes in patients.

The mechanisms underlying the development of autism are not yet known. Synaptic dysfunction, possibly implicating the transmitters glutamate or serotonin or a synaptic protein, is one of the major hypotheses concerning the mental dysfunctions observed in the patients. Structural abnormalities affecting neurons implicated in imitation have been reported, as has reduced intracortical connectivity and integration implicated in attention, orientation to auditory and visual stimuli, novelty detection, language and face processing, and information storage. The developmental abnormalities may alter neural cell proliferation, migration, survival, axon and dendrite extension, and synapse formation. The neurodevelopmental pathways that are dysfunctional in autism must be elucidated. All explanations of the physiological basis of autism remain at the moment hypothetical.

In the absence of a biological target, treatment of autism is mainly directed towards reducing the patient's deficits, improving quality of life and functional independence; psychotherapy, rehabilitation of social skills, speech and language, occupational therapy and educational therapy are some of the means. Antipsychotic drugs can be effective against behavioural disturbances, but with the same unacceptable side affects as in schizophrenics. No known medication relieves the core symptoms of the disorder, and progress is limited by the variability of the signs and symptoms of the disease and the lack of biological markers to evaluate efficacy. Symptomatic relief has been reported by deep brain stimulation in patients with Gilles de la Tourette syndrome and obsessional compulsive disorders, although its use in autism itself has not yet been envisaged. Other brain stimulation techniques might also be imagined, as in depression and schizophrenia, if the neural systems that subserve the functions that are altered in patients are intact. Most of all, the developmental processes that are disturbed by the disease need to be identified and, the biological substrates elucidated, so that effective, and particularly early, treatments can be devised to prevent or compensate for the deficits. For this, as in the diseases described above, the need to identify quantifiable biological markers of early autism are essential.

RESEARCH EFFORTS NEEDED

Research on brain-related diseases involves clinicians (neurologists, neuropsychologists and psychiatrists) who analyse patients, epidemiologists who identify vulnerable populations, molecular geneticists who discover causal genes, neurobiologists (cell biologists, biochemists, electrophysiologists, anatomopathologists), brain imagery specialists, bioinformaticians that model brain function, biostatisticians and other data processing specialists. The relative cost of their activities is quite variable, depending, among others, on the instrumentation needed. Their weight in the study of the different brain diseases also varies, depending on progress that has already been made.

Research on the primary neurodegenerative diseases like Parkinson's disease, Alzheimer's disease or amyotrophic lateral sclerosis, has progressed sufficiently so that specific and essential focuses for research have emerged; i.e. the molecular pathways that appear to be implicated in the physiopathology of the diseases and the identification of rational targets for therapeutic intervention. In a secondary degenerative disease, like multiple sclerosis, if such is indeed the case, understanding the mechanism of the primary autoimmune insult to be able to counteract its consequences is a priority. Basic research on the psychiatric disorders has progressed less far. This field of brain research has not received the same attention as have the neurodegenerative diseases, with their clearly biologically based pathology that is amenable to research on model systems. The symptoms of these diseases are broadly localized and highly variable, so that categorization of patients is still uncertain, and the physiological substrates of the various symptoms difficult to identify, making it difficult to address these diseases through experimental models, or to constitute the homogeneous cohorts needed for valid investigations. Research in these diseases will certainly benefit enormously from the development of structural or chemical disease biomarkers of the disease and high-resolution non-invasive techniques, such as functional imaging.

In all cases, more clinical research is needed for more precise classifications of patients, more genetic research is needed to identify disease-causing genes that give insight into the pathophysiology of the diseases and permit the development and of cellular and animal models for analysis and therapeutic advances, more access is needed to high-resolution in vivo imaging systems and other techniques for non-invasive analysis of brain function in patients, and more high-powered data analysis systems are needed to benefit from the research efforts. These points, among others, will be discussed in more detail in the following paragraphs.

A. COLLECTION OF DATA ON PATIENTS

Clinical observation of patients is the precondition for all research on brain-related diseases. It allows accurate diagnosis of patients, but also constitution of the large homogeneous cohorts of well-described patients needed to discover the genes implicated in hereditary forms of the diseases, to perform epidemiological studies that identify populations at risk, or to test preventive or therapeutic strategies.

1. Clinical analyses

Increasing the amount of data available for research and structuring the collection and storage of the data, eventually accompanied by collection and storage of tissue samples, are of

fundamental importance, to avoid wasted or duplicated efforts and to compensate for the dispersion of the medical and scientific community.

a. Increase research potential in Europe

For clinical information to contribute to a research effort, large cohorts of homogeneous patients are needed to obtain statistically significant results. This means bringing together data from a maximum number of patients. Data collection must be standardized, however, in terms of what is recorded and how it is determined, how diagnoses are made, how patients are classified, etc. This is already done *ad hoc* in the various networks and collaborative studies, particularly where molecular genetic analyses or epidemiological surveys are foreseen. Measures for bringing together clinicians, including those in private practice or clinical settings not associated with research environments, into networks with consensus as to how patients are examined and classified, should permit the collection of greater amounts of data in a form that is adapted to the exigencies of research. In addition to increasing the availability of cases for statistically valid studies, this would also propagate consensus on "best practice" for the benefit of the patients.

b. Data collection

The collection of the signs and symptoms of the different motor, cognitive, memory and emotional disorders, quantified by standard methods, including electrophysiological recordings and brain imaging, depending on the instrumentation available, should be encouraged. The genetic data required for research on patients with hereditary diseases and the members of families should also be systematically obtained. To be utilisable for research purposes, however, data collected on patients needs to be compared to data collected from matched control populations. While this is a fundamental part of any specific research protocol, for more general collection of data on healthy subjects could be the object of special campaigns. Ideally, the data could be collected, at least on standardized forms, and, at best, be fed into data bases, including specific imagery banks, maintained and accessible in conformity with the legal and ethical standards in use, and accessible for specific research programs, under conditions that need to be defined

c. Sample collection

Patient data collected at the clinical level can usefully be accompanied by tissue samples. In addition to blood samples for genetic research, samples of cerebrospinal fluid for biomarker identification, biopsies or post-mortem brain, should also be encouraged when authorized. To a large extent, molecular genetic research in brain-related diseases is indissociable from clinical research, in that the collection of well-characterized families and DNA/blood samples is done at this level. As for data collection, sample collection also requires the obtention of samples from appropriate control populations, although for ethical reasons, this can be problematic, but is an absolute necessity for successful research. It would be of help to develop an appropriate legal framework in which this can be done.

Sample collection for research purposes, even more than data collection, requires the application of standardized techniques. It must also be performed in accordance with local and international ethical regulations. The storage of the samples is a particularly difficult problem, and requires the creation of, or association with, state-of-the-art brain, tissue, and cell banks; unlike data which is permanent once stored, most tissues need stringent storage conditions to avoid alteration. The rules regulating access to the tissues is also a serious problem. There are a number of brain, tissue, DNA and cell banks of different sizes, private or institutional, in existence, who are actively

grappling with the problems of obtention, storage and access to biological resources. Lack of access to such material is a serious obstacle to research.

2. Genetic analyses

Molecular genetics, important for the diagnosis of hereditary disorders of the brain and the counselling of patients, is also an essential tool for studying the pathomechanisms underlying these diseases, even in their sporadic forms. In addition to the identification of genes responsible for Mendelian (or monogenetic) forms of brain disease, it has become more and more important to identify genes which work together to cause disease, modulate the expression of other genes, or confer susceptibility to disease. The effects of genetic and epigenetic regulatory mechanisms on disease expression are now known to need investigation, for example in the case of disorders in which abnormal brain development is suspected, or gene/environment interactions in diseases for which there is a genetic vulnerability to the effects of a particular social or physical environment.

In addition to permitting precise diseases diagnoses and patient classification, genetic analyses are vital for research in that they open a window onto the pathogenic mechanisms underlying the symptomatology of the disease, the analysis of which in most cases is a long and frustrating process. Rare are the diseases, such as epilepsies caused by mutations in ion channels regulating neuronal activity, in which the relationship between the mutant gene and the degeneration or dysfunction of particular cells is evident. Moreover, most familial disorders of the nervous system are genetically heterogeneous. The more genes that are identified for a given disease, the more insight they will provide into the underlying dysfunction.

Classical studies, in which disease-causing genes are identified by association with arbitrary markers distributed over the genome, require large well-characterized families, and are therefore dependent on patient recruitment at the local level. This should be encouraged, and should ideally be accompanied by valid epidemiological studies. More recent high-throughput screening and sequencing techniques allow analysis of the whole genome to identify single or multiple genetic variants that might predispose to a disease, without being immediately causal. The identification of modifying genes or genetic risk factors, gives previously unavailable insight into disease pathogenesis. These studies, which require an appropriate infrastructure, are just beginning to yield results. Modern molecular genetic research is machine- and labour-intensive. Already adept at the formation of project-related clinical consortia, networks and other multicentric research associations, development of more open but structured means of associating the material and the technology for high-throughput gene analysis (DNA banking, open or restricted access data bases, public or private technology platforms, outsourcing of analyses to biotechnology companies) would accelerate advances in this domain.

Equally important, however, are "post-gene" studies aimed at understanding the normal and pathological functions of proteins encoded by mutant disease-causing genes. The needs of this type of research, particularly the model systems that are most appropriate, will be discussed below.

3. Epidemiological studies

Epidemiological studies of patients with neurological or psychiatric disorders are imperative, because they underlie assessment of the impact of neurological and psychiatric diseases in populations, help constitute patient cohorts for identifying causal genes and genetic and environmental risks. Given the importance of this information for evaluating the weight of the

diseases on society, the way patients are treated, and the public health measures that might be taken to protect populations against these diseases, epidemiological studies are relatively neglected, and are not always methodologically sound, reducing their impact. Broad studies (national, European, international) performed with validated methodologies should be promoted, and training programs in epidemiology should be reinforced.

B. RESEARCH PERFORMED ON PATIENTS

Disease-related neuroscience research is performed at different levels of complexity (in the test tube, on cells, on animal models, on patients), by means that are in constant evolution. The most complex level is the patient himself, the only "model" in which the disease process, as it occurs in humans, can be studied. While fraught with difficulties because of the complexity of the human organism, and subject to ethical constraints, more and more highly informative data can be collected directly on patients, due to the development of powerful, high-resolution imaging and other non-invasive techniques of investigation, access to which is still too limited.

Research on patients is also problematic because of the difficulty of constituting cohorts that are sufficiently large and homogeneous (the neurodegenerative and psychiatric diseases themselves are particularly heterogeneous) to obtain statistically valid results. The development of means for bringing together compatible data obtained in different sites would help to overcome this problem. Studies that can be usefully performed directly on patients concern analyses of brain structure and function (sensory, cognitive, affective), the search for disease biomarkers. Difficulty in accessing the means to perform such studies is, however, an obstacle.

1. Brain structure

Study of brain structure in patients with neurological or psychiatric disorders compared to normal subjects is essential to link symptoms with abnormalities in the brain. The correlations can then be tested in models to determine causal relations. This is done either on post-mortem brain or on patients themselves with new techniques of brain imaging, transcranial magnetic stimulation, or electrophysiology. Both approaches have their difficulties that must be overcome to advance our understanding of the diseases.

a. Anatomopathology

Classical neuroanatomical and neuropathological studies on post-mortem human brain has long been the principal method for studying the structure of the normal and diseased human brain. It has been particularly successful in diseases in which histological abnormalities (e.g. Lewy bodies in patients with Parkinson's disease, neurofibrillary tangles or senile plaques in patients with Alzheimer's disease) can be detected. With proper precautions, cell loss and brain malformations can also been detected. The development of immunohistochemical techniques, in which proteins can be localised by the use of specific antibodies coupled to enzymes producing a coloured product or light, or fluorescent molecules such as the Green Fluorescent Protein and its derivatives, have greatly increased the amount of information that can be obtained on post-mortem brain from patients, as well as on cellular and animal models of the diseases. Progress has been made in the efficacy of such studies with the development of higher and higher resolution microscopes and markers that permit the detection of specific molecules, their associations and even to some extent their interactions. Research into these methodologies will provide even more informative techniques, and should be encouraged. These techniques are at some level accessible to, all

laboratories. The most technically advanced instruments needed for the analyses of these preparations (confocal, laser, bi-photonic, ...), however, are too costly for individual researchers or small groups, and are technically demanding, requiring assistance from dedicated personnel, most often in the form of platform or core facilities open to researchers, but implying the existence of large institutional structures. Access to such structures needs to be increased.

However, post-mortem brain is most often from very elderly subjects and represent the end stages of a long disease process that cannot be distinguished from compensatory changes that have occurred during its evolution Rather large collections of brains from patients with some neurological diseases exist, notably Parkinson's and Alzheimer's disease; there is little material for the systematic study of the psychiatric disorders. In any case, post-mortem tissue is subject to conservation (formol or freezing) artefacts. Most of all, they are rare and are becoming rarer still as autopsies are less and less performed; the corresponding controls are rarer still. Attempts are being made to improve access to post-mortem brain, notably campaigns by patient associations to promote autopsy, in collaboration with quality-controlled human brain banks that are trying to deal with the serious ethical problem and the multitude of organisational difficulties involved in large scale human brain-banking. Efforts should be made to increase the availability of this precious material.

b. Brain imaging, deep-brain and transcranial magnetic stimulation

The advantage of brain imaging techniques (positon tomography, functional and structural magnetic resonance imaging, ...) is that patients can be analysed at various stages of their disease. The resolution of the techniques has greatly advanced. The development of new markers of brain structure and function that can be used with these instruments will increase even further the value of this technology.

Deep brain stimulation with electrodes implanted in the brain, already used to treat Parkinson's disease may also be adapted to other diseases. In addition to its therapeutic effects, treatment of motor and eventually non-motor disease symptoms with deep brain stimulation provides important knowledge of the brain circuits involved in the diseases. However, how this technique works is not yet well understood. Investigations into the mechanism of action of deep-brain stimulation and into the possibilities of its use as a technique for research, especially on animal models, should be furthered.

Transcranial magnetic stimulation, which uses a magnetic field to carry a stimulating current across the skull into the brain, is used for studying the functional connections of brain neurons, and is thus of importance for understanding neurological, cognitive and psychiatric disorders, as well as for diagnostic purposes. Repetitive stimulation which causes long term changes in the effectiveness of synaptic connections, and thus the excitability of neurons, has potential therapeutic applications.

The equipment needed for these different techniques is costly, however, and requires specialized personnel, for operation of the instruments to obtain results, but also for analysis of the data. Research is hampered, however, by the relatively the small numbers of subjects that can be analysed, due among others to the computing and storage resources that are needed, and the relatively small number of places where this type of research can be done. Increasing the number of facilities where such work can be done, and organizing access to such facilities will advance our understanding of both the normal and the pathological brain.

2. Biomarkers

These are brain images or easily accessible biochemical substances that can be used to distinguish between normal and pathological states. They can be used for diagnosis, follow-up, and the monitoring of therapeutic effectiveness, as well as analysis of molecular mechanisms implicated in brain disease. They are particularly important for the early detection of brain diseases in the preclinical state, when therapeutic intervention might be possible to slow or stop the evolution of the disease. The search for biomarkers has been accelerated by technical advances in the "omics" (genomics, trascriptomics, proteomics, metabolomics, ...) and the development of high-throughput techniques for screening expressed genes and mass and molecular resonance spectroscopy, which allow the simultaneous quantification of a great number of molecules in tissue samples, and more usefully in body fluids (blood, urine, cerebrospinal fluid). These studies, which are in their infancy, permit multiple comparisons of patients and model systems, which enhances the possibility of obtaining valid results, but require sophisticated statistical analyses as well as computing resources. The identification of such markers is of major importance.

3. Cognitive function

Fundamental to the study of Alzheimer's disease and other dementias, including certain forms of Parkinson's disease, it is becoming clear that cognitive function is also altered in patients with psychiatric disorders, such as schizophrenia and the autism spectrum disorders, and even in depression, but not enough is known about cognitive dysfunction in these diseases, and what it can tell about the underlying brain disorder. Research into cognitive function in the psychiatric diseases needs to advance.

C. RESEARCH PERFORMED ON MODEL SYSTEMS

No model system exactly reproduces a human brain disease, even of a monogenetic disorder. However, all can offer insight into specific aspects of brain dysfunction; e.g.; the abnormal activity of a mutated protein or its toxic accumulation, insufficient mitochondrial activity, loss of a specific population of neurons, etc. They are the best one can do, however, to obtain the controlled conditions necessary for experimental manipulations, the results of which can then be verified on human post-mortem brain or by imaging or biochemical markers in patients. A variety of animal models of increasing complexity are available, each of which has its advantages and shortcomings: cells in culture, drosophila, fish, rodents, non-human primates, ...). Access to the different types of models, and the expertise needed to benefit from them, is therefore essential for fruitful research. It is important to find ways in which this can be facilitated.

The use of the cellular or animal models of diseases is driven by a hypothesis (exo- or endotoxicity, enzyme deficiency, faulty cellular transport, ...) or by genetic research, which plays an increasingly important role, as more and more causal genes for brain diseases are discovered. Of critical importance, especially for "post-gene" models of hereditary diseases, are the methods for introducing gene defects, or therapeutic genes, into the model cell or animal. The cloning of genes and the construction of vectors for producing transgenic animals has long been a relatively improvised time-consuming activity, for the needs of small often isolated research groups. Technical advances, however, can greatly improve the success of such models, controlling the time of expression of the gene, its insertion in the genome, etc. The organization of specialized public core facilities or private companies specialized in the production of vectors with diverse properties would be extremely useful. Such sources already exist to a certain extent, but are financially onerous. These essential tools should become more readily available. Furthermore, as for studies on

patients, better access to the most powerful analytic methods is necessary for advances to be made through the study of animal models.

1. Experimental models

a. Cells in culture

Cells in culture, proliferative cell lines, or primary cultures of neural cells, are the most easily manipulated of experimental models, although they have many drawbacks, including accumulation of changes with time, and the absence of essential intercellular interactions needed for cell survival and which may participate directly in the pathophysiology of many brain diseases. Furthermore, neurons are post-mitotic cells that do not proliferate, so that non-neural cells or neuron/glial hybrids that do proliferate are commonly used to study neuronal dysfunction, either with toxins or with vectors that produce genetically modified organisms mimicking the disease state. This is not ideal. Primary cultures of neurons from animal models are closer to the "reality of neural function, but do not proliferate, limiting the material available. Both types of cellular models, nonetheless, provide a great deal of information, which needs validation, however, in model neural systems closer to humans, or in patients themselves.

Much interest has been generated by recently developed techniques that permits the reprogramming adult cells (e.g. skin fibroblasts) to pluripotent stem cells (iPS cells) capable of differentiating into any cell type. This technique should provide the possibility of obtaining homogeneous populations of a specific type of neural cell, from normal individuals, but also from patients with brain-related diseases, and would represent the closest possible cellular model to the disease state. Conditions for producing the dopaminergic neurons that die in Parkinson's disease have been elaborated, and have raised hopes for their use in analytic or screening procedures, and for cellular replacement or gene therapy. As they reflect the genome of an individual, multiple cell lines will be necessary, as with patient cohorts, to overcome the effects of individual variation. This type of research should be fostered.

b. Small animals

Although severely regulated for ethical reasons, research on small animals is the major and inevitable source of knowledge on the pathogenesis and pathophysiology of neurological disorders, and will become even more so as the vectors used for producing genetically manipulated models increase their potential. However, whereas access to cell culture facilities is rarely a difficult problem to overcome, access to animal models is highly problematic. Small animals such the nematode, Drosophila and its many mutant fly lines are somewhat more problematic than cell lines to maintain in culture, and require much more specialized knowledge for their manipulation, but are excellent for genetic and biochemical screening techniques. The same is true for the zebra fish, a model becoming more popular, but is still rare, and access limited therefore posing the problem of collaborative efforts. The vast majority of animal research in disease-related neuroscience, however, is still performed on rodents, particularly mouse models of disease, produced with toxins (MPTP to produce parkinsonian mice, ...), by spontaneous mutation or by genetic manipulation. This requires large animal housing facilities for the production and maintenance of the animal lines as well as experimentation (surgery, pharmacological treatments, blood sampling, ... behavioural studies), that must be performed under strict conditions for hygiene and for the containment of the genetically modified organisms, and require qualified personnel for the administration of the facilities, care of the animals. Platforms to produce the models are needed, associated with phenotyping centres,

combining multidisciplinary expertise in physiology, electrophysiology, neuroimaging and motor, cognitive and adaptive behaviour.

c. Non-human primates

Various species of monkey have long been used for studies in neuroanatomical and neuropsychological research. The study of normal cognitive functions and their cerebral organization in non-human primates is useful for understanding the homologous functions in humans, as well as the anatomic and structural divergences. As for their use in the study of brain diseases, MPTP-intoxicated monkeys have been successfully used to study the structural and functional consequences of the loss of dopaminergic neurons in parkinsonian humans, and a transgenic monkey monkeys overexpressing the protein alpha-synuclein in the *substantia nigra* mimic a form of familial Parkinson's disease. Monkeys expressing the mutation responsible for Huntington's disease have also been produced. The use of primate models of depression or autism, as such, is technically difficult to envisage, although certain aspects of pathological behaviour (stereotypy, repetition, loss of motivation, faulty error detection, and other behavioural traits) could be advantageously addressed. It is thought that primate models would be more predictive in preclinical studies of new drugs than rodents; translation from rodents to humans beings has not been very successful. Whether the problems encountered in preclinical therapeutic trials in small animals are due to the species differences or to secondary problems has not yet been resolved, however, and the ethical issues concerning the creation and maintenance of sick primates need to be taken into account. Although non-human primate models will probably never be a primary research model, they are important to validate the results of studies on smaller models, before transfer to humans. There is, therefore, a shortage of centres in which anatomical, imaging and electrophysiological studies can be performed in awake primates.

d. Artificial models

Neuroinformatics, combining mathematics, physics, complex systems, information sciences, robotics and other technological disciplines is developing theoretical and functional tools to understand, model or mimic the functioning of the nervous system, from the simplest molecular and cellular level to the most integrated levels, such as the motor, sensory, motivational, mnesic and other cognitive functions. The use of entirely artificial models of normal adaptive and pathological brain function is a highly specialized and thus restricted domain of neuroscience research, and should be encouraged, for understanding both normal and pathological brain function, and eventually to compensate for disease- or injury-related motor and cognitive deficits.

D. TECHNOLOGY-DRIVEN RESEARCH

Technological advances are allowing questions to be addressed that were previously inaccessible. The understanding of the neurological and psychiatric diseases will be facilitated by pluridsciplinary research involving physics, chemistry, biology, informatics and participants from a wide range of backgrounds (academic, clinical and industrial) working together to make and use these advances. At present, three different fields have proven their importance in disease-related neuroscience research and need support or further development: so-called "omics" driven research; research on high-resolution imagery and nanotechnologies.

1. "Omics"

"Omics" technologies (genomics, transcriptomics, proteomics, metabolomics) are increasingly used to study of disease states, because they allow simultaneous assessment of multiple changes in patients or experimental systems without the need for an *a priori* hypotheses as to what might be changed. The tools for genomic research are the most advanced, and are facilitating the identification of disease causing genes. Proteomic research is highly promising but, because it looks for changes in the level of expression of the messenger RNA encoding the proteins or the levels of the proteins themselves (not necessarily correlated), it is extremely sensitive to differences in experimental conditions, and also needs particularly sophisticated statistical analyses to yield valid data. Metabolomics, the study of the metabolic state of patients or experimental models by chemical analyses of body fluids or tissues, is the newest of the "omics", but promises to yield important results, in particular the identification of quantifiable biomarkers of the disease states, markers that permit early diagnosis, as well as monitoring of the progression of the disease and the effects of therapeutic interventions. So far, there has been little correlation among the results obtained by different laboratories, so that a great deal more effort is necessary to standardize procedures, to produce the necessary analytic tools and the computational facilities necessary for analysis of the results, so that the vast amount of data produced by these techniques can yield valid results.

2. High resolution imagery and transcranial magnetic stimulation

Basic research in imaging techniques, be it the development of higher resolution (spatially and temporally) microscopes or brain imaging techniques, or more informative markers, radiotracers, contrast agents, etc., is of the utmost importance, especially for functional studies in patients, for monitoring lesions during the evolution of a disease, for evaluating the effects of new treatments and for the elucidation of their mechanisms of action. Indeed, for the psychiatric diseases, it is probable that progress will come from this type of studies. Since the questions that can be investigated in patients and models are conditioned by the research tools available, a great deal is therefore expected from research in this area.

Transcranial magnetic stimulation has been reported to affect neurotransmitter release, synaptic efficiency, neural excitability, neural plasticity, but also gene transcription and even neurogenesis. It has proved to be a useful tool for the analysis of the brain regions and motor circuits implicated in motor control, but also in cognition and affect. Most studies have been performed so far in patients with Parkinson's disease, who have motor, neuropsychological and psychiatric disorders, both to understand the disease and to evaluate the therapeutic potential of this technique. It has also been used in depression and, schizophrenia. The use of this technique both for analytic and therapeutic ends, ideally in association with functional brain imaging techniques or other biomarkers monitoring its effectiveness, needs to be encouraged.

3. Nanotechnologies

As for high-resolution imagery, developments in the nanotechnologies applicable to neurosciences (biological nanomarkers, microsensors, nanostimulators, brain-computer interfaces, etc.) will condition possibilities for high-resolution research, but also for the more precise delivery of therapeutic agents. Advances from nanotechnology laboratories and industries are needed to potentiate these developments.

E. EXPERIMENTAL THERAPEUTICS

Translational research is needed to derive effective therapeutic strategies from knowledge of the pathophysiological mechanisms underlying neurological and psychiatric disorders. Strategies for protecting cells from the disease process, regenerating lost neurons, or substituting for their loss, in particular by understanding and adapting the mechanisms of normal neural development and plasticity, are particularly important to develop.

1. Identification of new therapeutic targets, agents and delivery systems

Understanding the causes of neuronal death in the neurodegenerative diseases (toxicity, activation of a molecular cell death pathway, inhibition of a survival mechanism, whether intrinsic to the cell that dies or resulting from a disturbed intercellular interaction) or the defective neural circuits in psychiatric disorders (developmental abnormalities, molecular dysfunctions) are essential to the elaboration of effective treatments. Hypothesis-driven or unbiased genomic, proteomic and metabolomic research will help identify the molecular mechanisms that are dysfunctional in the different pathologies, offering innovative agents or molecular targets for therapeutic intervention. Vectorology and nanotechnology research will help find better ways of delivering the agents (small molecules, genes, cells, ...).

2. Gene and cell therapy

The development of vectors for the delivery of therapeutic genes (transgenes) or the elimination of deleterious genes (gene invalidation, inhibition, or modification by exon excision or replacement, ...) and the delivery of replacement cells (embryonic, genetically-modified, iPS-cell derived neurons, ...) is already an active field, but must be reinforced to obtain viable therapies. So far, the results in patients, when tried, have been disappointing. The mechanisms of neural development, neuron survival, proliferation, differentiation, neurite extension, synapse formation, adult plasticity, signal propagation, must become better understood. How to protect therapeutic cells from the ongoing pathological process in the host brain is a particularly important problem that needs to be faced.

3. Immunological therapies

There are two types of immunological approaches, both of which are promising. First is the use of anti-inflammatory agents to counteract disease mechanisms involving in immune system; e.g., methods of inhibiting the autoimmune attack on myelin in multiple sclerosis, prevention of immune response suspected to contribute to the propagation of neuronal death in Parkinson's disease. The second strategy involves generating, by vaccination or antibody administration, an immune response against the deleterious proteins that accumulate in a number of neurological diseases; research has advanced on the use of such a strategy in Alzheimer's disease, but might be applicable also to Parkinson's disease, frontotemporal dementias, among others.

4. Brain stimulation and brain-machine interfaces

Intra- and extracranial electrophysiological methods for modulating the electrical activity of the brain for therapeutic ends is a promising strategy that needs more research. Two basic types of intervention have been envisaged, one in which deep brain or transcranial stimulation, can be effective if nerve cell connections are essentially intact; the other, brain/machine interfaces, in

which brain activity can be mobilised to direct prosthetic devises when neural connections are interrupted.

a. Deep-brain and transcranial magnetic stimulation

Stimulation of specific regions of the brain with implanted electrodes has already been shown to be an effective, well-tolerated and reversible treatment for difficult cases of Parkinson's disease with debilitating side-effects, and is being explored for obsessive compulsive disorders (OCD and Gilles de la Tourette Syndrome, depression), and might be envisaged for other neurological, cognitive or psychiatric disorders. Much more needs still to be learned about how this technique works.

Promising results have been reported on treatment of the motor, cognitive and psychiatric symptoms of patients with Parkinson's disease, or hallucinations in schizophrenia, with repetitive transcranial magnetic stimulation, suggesting that this technique might, like deep-brain stimulation, also be applicable to other movement and psychiatric disorders, as well as dementia. Epidural cortical stimulation has been suggested to be possible alternative to both deep-brain and transcranial stimulation. All of these techniques need further research to understand their mechanisms of action and to determine the parameters that might lead to their effective use in the treatment of brain disorders.

b. Artificial neural networks and brain/machine interfaces

Neuroinformatics research is developing artificial neural networks inspired by the brain or prosthetic devices utilizing the brain's natural plasticity, that can alleviate sensory or motor handicaps resulting from injury or disease. The interactions between the neurologists, neuroscientists, physicists, information and robotics specialists required for the development of these need to be organized and encouraged.

c. Learning-based therapies

The molecular and cellular mechanisms that underlie learning by the brain need to be better known. Theoretical research on machine learning can contribute to this understanding. The insights into how brain plasticity can be adapted to the remediation of strictly educational problems, but also to the treatment of behavioural disorders, as in autism, where preliminary studies indicate that self control, for example, can be increased. The development of an application to the treatment of cognitive deficits, as in patients with dementia or at risk for developing dementia, might be envisaged.

F. PREVENTION

Prevention of the neurodegenerative and psychiatric diseases is a field of research that is not sufficiently developed, but which could have an important impact on the prevalence of these handicapping disorders.

1. Identify genetic risk factors

The most straight forward approach is the identification of genetic risk factors for the different diseases (causal genes, modifying genes, susceptibility genes). Genetic research into all of these diseases is therefore to be encouraged.

2. Identify environmental risk factors

The identification of environmental risk factors (social or physical) can be directed by both epidemiological studies or by prospective analysis. The social factors thought to contribute to the psychiatric disorders need to be better and more systematically studied, as well as the genetic predispositions that underlie vulnerability to these factors. Analysis of the role of environmental toxins in brain-related diseases is clearly much needed, given the variety of known and potential neurotoxins to which human beings are exposed. That environmental toxicity, due to pesticides for example, can cause Parkinson's disease is well established. Toxic food substances are also suspected to cause disease, as in atypical Parkinson's disease in Guadeloupe. Systematic and well controlled research into the neurotoxicity of the many air- or food-born pollutants to which humans are exposed is urgently needed.

CONCLUSIONS

In addition to the disease-specific questions that need to be addressed by research, and the development of new analytical and therapeutic tools, two important general needs for research have emerged. First, progress in research on brain-related diseases is more and more dependent on access to sophisticated instrumentation (high-resolution microscopes, brain imaging equipment, mass spectrometers, magnetic resonance spectrometers,.....) and infrastructures (animal houses, tissue and DNA banks, facilities for large scale "omics" analyses, ...facilities, ...) that are beyond the means of individual research groups, and require highly specialized personnel; the analytical power of these technologies is inversely correlated with their accessibility to the research community. Secondly, the large amounts of data that will be collected would best be analysed as a whole, requiring shared data bases and computational resources, biostatisticians and informatics experts, ...). This is a utopian aim, but is also a priority, if the data collected is to be fruitfully exploited.

Research, mostly performed by small research teams working in relative isolation over large geographical areas, is necessarily fragmented. Individual creativity is encouraged by this organization. However, the multidisciplinary studies that would be most productive will be performed in a smaller number of large centres of excellence that provide the instrumentation, infrastructures and specialists in the most advanced disciplines. A certain number exist, and more are needed. The question is how to open these centres to outside researchers. The answer probably lies in organizing the convergence of public and private research institutions, and outsourcing to specialized biotechnology and pharmaceutical companies, necessary for efficacious multilevel and interdisciplinary research and its translation into therapeutic advances.

EXECUTIVE SUMMARY

Neurodegenerative and psychiatric disorders are responsible for a third of disease burden in Europe, for a cost of 386 billion dollars a year. A major part of the burden is due to six neurodegenerative (Parkinson's disease, Alzheimer's disease, multiple sclerosis) and psychiatric (depression, schizophrenia, autism) diseases for which there is still no cure. Research on brain-related diseases aims at elucidating the causes of brain dysfunction in patients and the underlying molecular mechanisms, knowledge of which necessary for the development of innovative treatments. What kind of research is needed and what is required to perform this research effectively are the questions addressed.

I. What research is needed ?

A. For the neurodegenerative diseases:

- Study of the toxicity of abnormal protein aggregates and their cell-to-cell propagation in the pathogenesis of the diseases, and their possible neutralisation by immunological agents (vaccines, antibodies, ...);
- Study of the role of the immune system in the propagation of cell death in populations of vulnerable neurons;
- Understand the mechanisms of neuronal survival, neural development, myelination and synaptogenesis, their defects in brain-related diseases, and the development of therapeutic strategies to correct them.

B. For the psychiatric diseases:

- Better analyse disease symptoms, especially cognitive dysfunction;
- Identify brain lesions and/or abnormal neural circuitry in patients, in particular through high-resolution non-invasive techniques, such as functional imaging or extracranial stimulation.

C. For all brain diseases:

- Genetic research to identify causal genes or susceptibility factors that give insight into the pathophysiology of the diseases and permit the development of cellular and animal models for analysis and therapeutic advances;
- Epidemiological and toxicological studies to identify social or chemical (air- or food-born pollutants) environmental risk factors.
- Identification of quantifiable biomarkers (brain images or biochemical substances that distinguish the normal from the disease state, even in the preclinical phase), for diagnosis, monitoring of disease evolution and evaluation of the effect of treatments.
- Develop the techniques of intra- and extracranial brain stimulation for investigative and therapeutic applications in patients and animal models;
- Promote translational research to identify new therapeutic targets and agents based on unbiased "omics" (see below) studies and hypothesis-driven research.

II) What is needed to perform the research effectively

A. Research on patients

- Development of large data bases for the collection of standardized clinical and genetic data on patients from different centres, even private practice, to create the large cohorts needed for genetic, epidemiological, pathophysiological research, and organisation of access to the data.
- Collection of biological samples from well-documented patients and the development of biological resource banks (blood, DNA, cells, LCR, biopsies, brain tissue, ...), which can be readily accessed for specific research programs.
- Development of data bases for the collection and analysis of brain images from living patients and organisation of access to the data.

B. Research on model systems

- Development of transgenic small animal models (nematode, drosophila, zebra fish, rodents, ...) of the diseases, the molecular technologies necessary for their creation, facilities for producing, raising and distributing the animals, and multidisciplinary phenotyping platforms to study the physiology, electrophysiology, neuroimaging and motor, cognitive and adaptive behaviour of the animals, as well as preclinical therapeutic studies;
- Promotion of centres for research into cognitive and motor disorders in non-human primates, particularly anatomical, imaging and electrophysiological studies on awake animals, and for preclinical testing of innovative therapeutic strategies.

C. New technological advances

- Develop the techniques of high resolution brain imaging, transcranial magnetic stimulation, and deep brain stimulation, for both the study and the treatment of patients;
- Promote the development of high resolution microscopic techniques and markers for anatomopathological studies and their accessibility to the scientific community;
- Further the development of high throughput genomics, transcriptomics, proteomics, metabolomics techniques (transcriptomics platforms, NMR and mass spectroscopy) for assessment of multiple changes in patients or experimental systems, the data bases needed to collect and manage the data and the biostatisticians to treat the data;
- Explore the safe use of nanotechnologies to develop microsensors, stimulators, brain computer interfaces, nanomarkers, etc., and vectors for drug delivery and the potential of stem cell therapy;
- Translational research to develop therapeutic strategies based on the pathophysiological mechanisms underlying the neurological and psychiatric disorders;
- Pluridisciplinary neuroinformatics research to develop artificial models to understand normal and pathological brain function and brain-machine interfaces to compensate for disease- or injury-related motor and cognitive deficits.

ANNEXE 1: Bibliographic Reviews

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ANNEXE 2 : Interviewees

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