*French Republic*

PARLIAMENTARY OFFICE FOR SCIENTIFIC AND TECHNOLOGICAL ASSESSMENT

# IMPACT AND CHALLENGES OF THE NEW BRAIN EXPLORATION AND THERAPY TECHNOLOGIES

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*Over the past fifteen years or so, progress in neuroimaging has led to extraordinary advances in neurosciences. This revolutionises the understanding of the brain, in the medical and fundamental research fields, but is causing tensions of an ethical, philosophical, legal and social nature.*

## A PUBLIC HEALTH PROBLEM

Brain dysfunctions are one of the primary causes of disease or handicap. According to the World Health Organization (WHO), they concern one in four people worldwide, represent today five of the ten main causes of handicap, and are reported to lead to 35% of expenditure on disease in general. Further, certain unassessable costs, such as the indirect impact on the patient's family or fall in productivity of people suffering from affections not causing a permanent handicap, are to be added to that percentage. Yet the average world expenditure in this sector is still lower than 3 dollars per inhabitant per year.

In Europe, each year 38.2% of the population, i.e. 164.8 million people, suffer from brain pathologies. Their total cost, estimated in 2004 by the European Brain Council (EBC) at 386 billion euros, reached 798 billion euros per year in 2010.

In France, although nearly one in five citizens have been or are affected by a neurodegenerative disease, it is difficult to gain support for prevention, follow-up and treatment over the long term.

## RESEARCH INTERNATIONALISATION

Major international research programmes, in which French teams are participating, are being implemented, such as the controversial Blue Brain project aimed at creating a virtual brain and which is being funded by the European Union to the extent of 100 million euros per year for a ten year period. The United States, Japan, and Germany are taking great action against neurodegenerative diseases owing to the ageing of their population; the same applies in France whose research enjoys great prestige internationally. The grouping of research bodies within the Alliance pour les sciences de la vie et de la santé (AVIESAN – Alliance for life sciences and health), and the Programme d'investissements d'avenir (programme of investments for the future) in neurosciences should increase this potential, if interdisciplinarity is promoted and if the traditional French divide between neurology and psychiatry is managed to be reduced.

The major research poles in France are all very recent and well recognised abroad: NeuroSpin, the Institut du Cerveau et de la Moëlle épinière (ICM – Brain and spinal cord institute), the Campus CLINATECH in Grenoble, the Centre de neurosciences de Lyon, and the Pôle 3 C and Hôpital de la Timone in Marseille... Scientists are satisfied with the share given to neurosciences in the investments for the future, but point out that the organisation, and above all the funding of research projects, lack clarity. The return to France of postdoctoral fellows, researchers and even institution directors should moreover be encouraged by better adapted and far superior work and pay conditions

In another respect, the transposal scheduled for 1 January 2013 of the European directive of 22 September 2010 on the protection of animals used for scientific purposes is likely to slow down research. European states including France will have to find the means of reconciling the requirements of protecting non-human primates and research in this field.

## INCREASING THE MOBILISATION OF RESEARCHERS

Despite global mobilisation and although effective neuroimaging shows the evolution of some neurodegenerative diseases or predicts their appearance, it has not yet allowed the development of new molecules; major pharmaceutical groups are not very involved, unlike imaging and robotics manufacturers. There are no or very few new drugs. This situation is leading to questioning and debates on the risk/benefit ratio in the development of new treatments for highly invalidating neurodegenerative or psychiatric diseases.

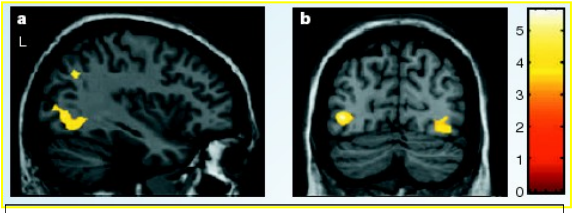
In France, efforts must be made to combat psychiatric pathologies which, poorly known, cause fear, rejection, and disgrace and are associated with insanity and violence. 74% of the French consider schizophrenics to be dangerous whereas only 0.2% of the latter represent a risk

to others. In France, there is no psychiatric epidemiology, nor any medico-economic or public health data. Psychosis prevention programmes exist in various countries in Europe, in North America, Australia and Japan, but France has fallen ten to twenty years behind with no prevention of psychiatric disorders. This is evidenced by the lack of preventive action targeting the impact of the use of cannabis in the occurrence of schizophrenic frenzy. The management of patients affected by mental diseases must be strengthened in France at all levels to combat the stigma they suffer. This can be achieved by means of targeted information and prevention campaigns, and systematic statistical studies on the pathologies concerned. It is clear that interdisciplinarity must be promoted in the approach to these pathologies, by strengthening the ties between the community of researchers and patients' associations, and by creating a multidisciplinary institute devoted to research on mental diseases.

## RECENT TECHNOLOGICAL PROGRESS

This progress consists in the development of instruments to increase resolution, and improve the reliability of data analysis and the conditions of data storage. Various approaches and technologies are used, often complementary and combined.

The possibility of seeing the brain operating thanks to magnetic resonance imaging (MRI) has radically changed the study of the brain on the scientific, therapeutic and even philosophical planes. The progress achieved in MRI is related to speed, resolution and multimodality. Multimodal imaging is used in the management of

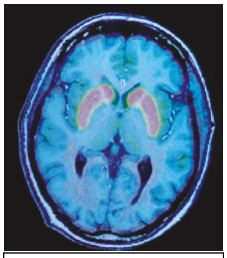



*Brain activity images (fMRI)*

malignant tumours and brain cancers, diffusion MRI helps visualise an ischemic accident within hours of its occurrence and in the future, and very high magnetic field MRI will improve resolution at the level of the cortex to better analyse its structure and detect any atrophies.

Positron emission tomography (PET) produces a functional image of some brain zones with molecular level precision; it is used for physiological or physiopathological studies on cognition and behaviour, as well as for the study of various pathologies affecting the central nervous system. PET is often coupled with an X-ray scanner. Recent evolution consists in combining PET and MRI. MRI helps locate and analyse complex neuronal mechanisms and PET allows molecular analysis of brain function; observation and exposure times are therefore lessened. However, specific skills and appropriate training are required to interpret the data collected.

The use of electroencephalography (EEG) combined with data processing systems and video increases the precision of analyses, which is very useful in detecting and treating epileptic seizures.



*PET image*

Some technologies combine the use of neuroimaging and intervention on the brain in a more or less invasive manner, raising ethical issues as some techniques may sometimes induce behavioural changes in patients. This is the case of deep cerebral stimulation, which consists in implanting, in an internal region of the brain, a high frequency stimulation electrode, the activation of which is controlled by the patient. This current treatment of Parkinson's disease is undergoing trials in the treatment of some drug-resistant disorders such as obsessional compulsive disorders, Gilles de la Tourette syndrome, or even deep brain depression.

Thanks to brain/machine interfaces, thought can control movement and conduct a machine. This way a person can manage to communicate without bringing into play his peripheral nerves and muscles.

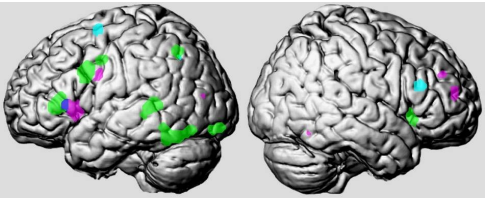
By three dimensional (3D) simulation of a specific environment where the patient is immersed and where he feels he is moving, positive effects are obtained that are validated in the treatment of some phobias, resistant pains, and in directing the movement of artificial limbs.

## STRENGTHENING PERSONAL PROTECTION

**Regarding the innocuousness of neuroimaging**, the Nuclear Safety Authority (ASN), which monitors the medical applications of ionising radiations, is concerned over the higher risks caused by the increase in medical imaging doses, the repetition of scanner examinations and the emergence of individual radiosensitivity. Furthermore, in France there is the difficulty of access to MRI machines in insufficient number (8 machines per million inhabitants, as against 35 in the United States and 40 in Japan) which leads too often to using scanners instead of MRI machines for brain exploration. Patients must therefore be informed of the annual radiation dose received. Also the number of MRI machines in France should be substantially raised and the number of radiation physicists should be increased, while improving their training.

**As for the reliability and interpretation of data**, precision depends to a great extent on the machine, the operator and the preparation of the patient. The measurement scale is often insufficient with MRI procedures performed at 1.5 Teslas (the most current ones). It is therefore tempting to increase the strength of the magnetic field to obtain clearer

images. Interpreting the results is tricky: sometimes, for one and the same person, and using the same machine, an inexplicable variation in the image is seen after very little interval time. A first source of variability may result from the machine itself, another from interferences during data collection (signal, signal/noise ratio, temporal drifts, artefacts, possible movements and discomfort of the patient in the machine). Any movement of course influences the signal. Further, the plasticity and short-term adaptation capacity of the brain through learning



processes can lead to a difference in cerebral activity recorded for a task performed at time T, then at time T+1.

The diagram below, with reading in green, calculation in blue and executive functions in violet, emphasises the complexity and multiplicity of the neuronal networks intervening in learning processes.

Account should be taken of variability and complexity in modelling and interpretations, the greatest prudence being necessary when it comes to rash extrapolations based on experiments limited to cohorts that are too small; each individual must be apprehended in his singularity.

## IMPROVING DATA PROTECTION

Neuroimaging has to use computing: images and data are regularly exchanged by this means between professionals owing to their complexity, especially to give an opinion on their interpretation; this is not without risk for their protection. The multiplication of exchanges raises the issue of the suppression of sources and data anonymisation. Personnel sometimes give precise information, without checking the identity of those asking them for it, and break medical secrecy without realising. A problem also arises with the electronic transmission of social security treatment forms as the social security nomenclature can allow the result of medical examinations to be known, especially the analysis of a neuroimage since the codes differ depending on the diseases treated. The Commission nationale de l'informatique et des libertés (CNIL - Commission on information technologies and liberties), while assuring it has obtained an improvement in the coding of information, acknowledges it is not sure about the security of the encoding processes. The coding and security procedures of databases must therefore be strengthened, the access of the personnel authorised to access them should be traceable, the training and awareness of medical personnel must be improved regarding compliance with medical secrecy, and the CNIL's means of expertise must be enhanced. Similarly, data-hosts hosting data on the health of the large cohorts necessary for research on neuropsychiatric diseases must be subject to strict approval conditions and must ensure secure hosting of the data concerned. The use of servers located abroad or of cloud computing forms a danger which justifies the adoption of a new international convention framing the circulation of medical information.

Excessive regulation must not however lead to killing innovation. In this respect, the recent Act of 5 March 2012 on research involving the human being is an excellent balance between respect for individual freedoms and improvement of research conditions, which should facilitate the work of French researchers.

## RIGHT TO KNOW OR NOT TO KNOW

The gap between the possibilities of precocious diagnosis and treatment capacities is widening more and more, leading to questioning on the very meaning of prediction and its interest. A plethora of questions arises. What should be done when a pathology is discovered fortuitously in a person in good health? The bioethics Act of 7 July 2011 partly settles the tricky problem of the right to know or not to know, and deals with the issue of informing parents when a genetic anomaly is discovered. The text strives to reconcile the rights and duties of each party and should serve as a reference; yet it would be necessary to rapidly publish the implementing decree of the Act on the definition of good practices applying to the prescription and performance of brain imaging examinations for medical purposes. Guides of good medical practices should also be drawn up providing tailored information for patients and persons accepting to undergo treatments or investigations involving imaging.

## RECOVERING OR INCREASING CAPACITIES

Neuroimaging and neurosciences raise several questions. Where is the border between action aimed at the recovery of body functions and that aimed at their improvement, what are the risks of behavioural changes, and what is the value of enlightened consent in borderline cases? The notion of enlightened consent for patients affected by slight behavioural disorders must therefore be clarified, and a guide of good practices in ethical terms must be drawn up on the use of brain implants.

Some stimulation techniques and some drugs developed for specific pathologies may be diverted from their primary use with a view to the technical or chemical improvement of personal capacities (extended wakefulness, enhanced attention and concentration capacities, through excessive consumption of psychotropic drugs). The Agence de la biomédecine (Biomedicine Agency) must therefore be rapidly given the means to exercise the new powers of monitoring and controlling neurosciences entrusted to it by the above mentioned Act. Only appropriate information and health monitoring by the Agence nationale de sécurité du

médicament et des produits de santé (National safety agency for drug and health products) and by the Biomedicine Agency can avoid the generalisation and negative forces of these practices encouraged by a performance-based society.

## USING IMAGING OUTSIDE THE MEDICAL SPHERE

Outside the scientific and medical sphere, the development of neuromarketing is raising a problem. Neuromarketing has developed from a misuse of neuroeconomics, a discipline located at the intersection of microeconomics, life sciences and imaging. Its goal is to understand the processes, sensations and action in a situation where a person must take a decision. The techniques and knowledge derived from neurosciences are applied by neuromarketing to consumer behaviour and it bases itself essentially on magnetic resonance imaging (MRI) to analyse what happens in the brain when an advertisement is watched or when a purchasing decision is taken. Such commercial experimentation mobilises for hours on end consumers, MRI machines, technicians and even neurologists. The validation of advertising campaigns by the use of MRI machines should therefore be banned. These machines should be reserved for treatment and scientific and medical research.

As for the use of neuroimaging in justice, frequent in the United States, it appears to be spreading to other countries like India and Italy. However the limited reliability of neuroimaging techniques provides little incentive to American justice to use it as evidence for prosecution; neuroimaging is used rather in support of the submissions of the accused. In France, the bioethics Act of 7 July 2011 frames the applications of neurosciences by regulating access to brain imaging techniques. It also creates a protective framework for human rights based on the major bioethical principles laid down in the code of civil law. The new Act limits the use of neurosciences and neuroimaging to three fields on the basis of three aims recognised as legitimate: medical treatment, scientific research and judicial expertise. The judicial aim introduced and limited to judicial expertise appears premature given the lack of reliability of the techniques. This provision is controversial and appears counterproductive in the present state of knowledge on brain imaging. It should not be allowed to decide on the guilt and the possibilty percentage of reoffending of an individual on the sole basis of neuroscience data. Expertise in the field will raise more questions than it provides answers. However the power of simplification and fascination of images and their scientific nature can influence, granting them probative value higher than what they are in a position to offer, and leading to misuses in the recruitment and insurance fields. The above -mentioned Act does not sanction the risk of specific discrimination resulting from the use of brain data, whereas it would have been easy to draw inspiration from the criminal sanctions applying to discriminations based on genetic characteristics. The protection of persons against these risks should therefore be strengthened by a regime of appropriate sanctions; the use of brain imaging in justice should be limited or even banned.

The convergence of technologies is bound to broaden. The ethical aspects and analyses relating to the societal impacts of this convergence must be updated by the OPECST (French Parliamentary Office for Scientific and Technological Assessment), which has already addressed this topic on several occasions, in particular in its work on nanotechnologies.

## INFORMING CITIZENS

The many personalities heard all emphasised the need to provide the public with information of a more scientific nature and better quality on the contributions of neurosciences and the evolution of the possible treatments of neurological and psychiatric diseases. All insist on the perverse effect of sensational information leading to the belief in discoveries paving the way to treatments. We are indeed still often far off such treatments. The brain does not operate in colour, the images are merely coloured artefacts resulting from mathematical models. The speed with which neurosciences and brain imaging have gained ground not only in the field of medicine and human and social sciences but also in everyday life is giving rise to fears and misunderstanding but also fascination. Therefore, while it lies with Parliament to make reform proposals, our fellow citizens must be informed of ongoing evolution in these fields by the organisation of public debates. Bioethics education must be provided at secondary schools and meetings must be organised between citizens and researchers to debate on the progress and limits of research in neurosciences. The OPECST will take part in them while pursuing its studies and warning work on all these issues.

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**The report is available at the following address: http://www.assemblee-nationale.fr/13/rap-off/i4469.pdf**

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