Presidenza del Consiglio dei Ministri

CNB

COMITATO NAZIONALE
PER LA BIOETICA

NEUROSCIENCE AND HUMAN EXPERIMENTATION: BIOETHICAL PROBLEMS

17th December 2010

PRESENTATION

The advancement of neuroscience and neurotechnologies consents to carry out experiments on humans, of low invasivity, aimed at a better understanding of the functioning of the brain and its relationship with thought and behaviour. These experiments have made a significant contribution to the debate in the scientific and cognitive context, and spurred a renewed philosophical debate on free will and attracted the interest of the public.

The NBC - recognizes the importance of such research and studies that will enable a better understanding of the relationship between emotion and rationality in human decisions as well as the correlations between the areas of the brain/thoughts /actions – and highlights the problematic elements related to the reliability of results, the ability to extrapolate generalizations and the interpretation of results. In this sense the need to take a critical view of these experiments and calls for scientific communication - both by the investigators and the media – which is able to draw attention in a balanced way to the novelties and restrictions of applications, with particular attention to the dangers of neurological reductionism and determinism.

The NBC highlights the need for these tests to be submitted to the attention of ethics committees and to the ethical requirements of each trial (the risk-benefit assessment, and free and informed consent, preceded by appropriate counseling; the balance between protection of *privacy* and societal needs).

Finally, the Committee calls for amplification of interdisciplinary comparison and proper public debate – as reiterated also in European and international documents - to increase the understanding of citizens, and promote critical scientific information, that is objective and well founded.

The document addresses a specific topic within the large theme of 'neuroethics'. It was drawn up as part of a working group on the basis of a text prepared by Profs. Lorenzo d'Avack and Laura Palazzani. Profs. Salvatore Amato, Adriano Bompiani, Francesco D'Agostino, Antonio Da Re, Silvio Garattini, Marianna Gensabella, Laura Guidoni, Assunta Morresi and Andrea Nicolussi have contributed to the discussion and drafting of the final text.

The document was approved by a large majority, with the votes of Profs. Salvatore Amato, Luisella Battaglia, Adriano Bompiani, Stefano Canestrari, Cinzia Caporale, Francesco D'Agostino, Bruno Dallapiccola, Antonio Da Re, Lorenzo d'Avack, Riccardo Di Segni, Emma Fattorini, Romano Forleo, Anna Gensabella, Aldo Isidori, Assunta Morresi, Andrea Nicolussi, Laura Palazzani, Vittorio Possenti, Lucetta Scaraffia, Monica Toraldo Di Francia, Giancarlo Umani Ronchi. Both Profs. Claudia Mancini and Demetrio Neri voted against. Prof. Grazia Zuffa abstained.

The President
Prof. Francesco Paolo Casavola

DOCUMENT

Premise

The considerable advances in neuroscience are increasingly subjected not only to the attention of bioethicists, but also to public opinion often in exaggerated and crude ways. Given the breadth of literature on these issues of a strongly specialistic nature but which are also of interest to the public and the speed with which the theoretical framework changes, the NBC limits itself, at present, to offering some preliminary observations on the relationship between human experimentation and bioethical issues, reserving the right to return to other issues, already partly discussed successively in the working group, (enpowerment, posthuman, robotics, criminal law etc.). This document is in line with other NBC documents on the subject of human experimentation[1].

1. Introduction

1.1. Advancement of neuroscience and neurotechnologies

The advancement of knowledge in anatomy and microanatomy of the nervous system and neurobiology together with technical advances in the development of methodologies and tools for the study of human brain (the so-called imaging techniques or neuroimaging) have allowed a rapid expansion of neuroscience research in relation to the diagnostic and therapeutic potential provided for the understanding of diseases. Research and results in this sector have attracted great interest also in the field of philosophy and bioethics, giving rise to wide reflection and discussion referred to as' neuroethics`[2].

Until a few decades ago, knowledge of brain function was limited because it was based on neurophysiological experimental techniques applied to animals (non-human primates and other mammals) - with significant bioethical issues due as to their extreme invasiveness[3] - by inserting electrodes into the cortex and recording of neurological functions in the execution of certain perceptual, motor or cognitive tasks. To this method there has been added the study of lesions induced on a particular area of the brain and analysis of the resulting behavioral deficits.

The transfer to humans of knowledge obtained from animal models can only be partial: it can not cover the more complex functions such as language, which characterize the human brain.

A more careful study of human complex cognitive functions (the field of neuropsychology and cognitive science) has been possible through the knowledge acquired by direct electrical stimulation of the cerebral cortex during

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[1] *The improper use of placebo,* 2010; *Secrecy in drug regulatory system procedures,* 2010; *Bioethical problems in clinical trials with non-inferiority design,* 2009; *Pharmacological trials on women*, 2008; *Drug experimentation*, 1992.

[2] It should be distinguished from 'applied neuroethics', which deals with ethical, social and juridical issues that may arise when the findings about the brain are reflected and used in clinical practice, social policy and law, from ' philosophical neuroethics 'regarding the philosophical and anthropological reflections of those lines of research aimed at investigating the neural bases of moral behavior.

[3] See an earlier NBC document *Alternative methods, ethics committees and conscientious objection to animal testing* 18th December 2009.

neurosurgical operations and the anatomo-clinical correlative method between the site of the lesion and resulting cognitive deficits. The introduction of methods of radiological study of the structure of the brain in vivo has since allowed more precise localization of the damaged site, which has pushed forward - indirectly – also the study of mental and psychological activity. Despite these radiological developments, the neurological study of the human brain needed adequate means of "visualization" of brain activity in vivo, capable of measuring brain activity in healthy individuals during performance of various tasks.

To facilitate these advances have been the combined achievements in the basic knowledge of cellular activities and the neural network (neurobiology) and development of imaging techniques applied to the study of human brain activity. While on the one hand some of these techniques have allowed the definition of disease with identification of damage in specific brain areas, on the other hand the development of specific methods using complex mathematical and physical tools, now allows study of the mechanisms of connection between neurons and the location of areas dedicated to specific functions. Both are of particular importance: the study of signal propagation and the connections between neurons (biological neural networks).

1.2. Experiments and studies

The availability of many new complex morphological and functional technologies with which to better recognize some brain circuits, characterized by low invasiveness, allows to perform experiments on humans aimed at a better understanding of the functioning of the human brain and its relationship with cognitive functions and normal and pathological behavioural aspects. The development of this kind of knowledge on healthy individuals, which is one of the goals of neuroscience today - as evidenced by the proliferation of contributions to psycho-neuro-biology magazines - is the aspect that may be more critical in terms of bioethics, while the development of knowledge with therapeutic or diagnostic purposes is part of the longer-established clinical trial.

In general, the experiments in question use a variety of modern technologies (see Appendix) that are intended to describe and / or measure the behaviour of individuals or groups of neurons in a given brain area or the relationship between two or more brain areas. This research is aimed to investigate in healthy or sick individuals, for example whether certain choices of behavior are the result of immediate automatic reactions or mediated/rational responses, as well as the relationships between emotional responses or cognitive capacity and stimulation induced by the environment. The experiments may involve the identification of brain areas involved in the dynamics of development of a decision or a moral judgement or changes in the brain induced by the experience of moral pain, forgiveness, and altruism. Also important is the research on changes in the brain in relation to violent or antisocial conduct and in relation to the capacity of discernment or the ability to distinguish between the assertion of truth and falsehood. Particularly relevant are the studies that aim to characterize the activity of specific brain areas in individuals unable to interact with other people or the environment, such as those in a vegetative state or minimally conscious. These and other issues can

be studied in relation to variables such as gender difference, socio-cultural diversity as well as different psychological profiles.

1.3. Problematics of research

Even though such experiments and research on the brain / thought / behaviour relationship have made a significant contribution to the resultant research and debate in scientific and cognitive fields, have prompted a renewed philosophical debate on ancient questions (such as the 'brain-body and mind-body 'relationship or the subject of freedom and free will) and have attracted interest from the public, in scientific terms, many perplexities have been put forward.

Experimental research generally takes place under very 'controlled' conditions, creating problematic elements in terms of their repeatability. These assume greater importance in neuroscience, for various reasons. Among these:

a) the choice of subjects is predetermined by criteria, which in itself can affect the outcome of the experiment and are not necessarily representative of the population;

b) subjects involved in a study often do not act spontaneously, but are instructed to collaborate with the experimental method (often the large number of tests required can transform voluntary movement into automatism rendering the study unreliable);

c) learning of the experimental details can cause anxiety that can interfere with results;

d) the representativeness of the sample is often insufficient to achieve adequate statistical analysis;

e) individuals think and act in 'artificial' situations far removed from reality;

f) the studies refer to the actual subjects however the conclusions of the studies are generalizations that do not consider/can not consider with precision individual variability (because of the plasticity of the brain, different environmental influences) and the variability of the same individual over time.

From these sample data one understands - although it does not detract from the importance of individual experiments - the difficulty of extrapolation and generalization, since the current phase of the research is still at a descriptive level: the results are still uncertain, and only in time can they be further validated by a more adequate scientific maturity. Therefore, the possibility of generalizing experimental data should be defined from time to time, drawing attention to the limits of application to reality. The constant exercise of critical spirit must still be accompanied by an attitude of openness with respect to these experiments, without the fear that may change acquired convictions.

In addition to the problematic nature of the experiments, the problematics related more specifically to the interpretation of results should also be noted, with particular reference to the 'correlation' between areas of the brain, thoughts and actions / performance of man’s duties. One must distinguish different meanings of 'correlation': correlation as exclusively deterministic causation, according to which there is a single, total and predetermined cause of one event or more causes that are necessary and sufficient for the same event (unique cause/effect relationship); correlation as a multifactorial causation, which admits the possibility that an event-effect may have multiple

causes, i.e. causes of various kinds (physical and non-physical). Within this latter sense it is possible to highlight relationships that are more or less statistically significant between the various causes and effects, never established a priori but only associated a posteriori.

The fact that a particular brain region, as evidenced by *neuroimaging*, is activated with particular intensity during the formulation of a thought or performance of a specific task, does not infer with certainty that this is the only region involved or the only one responsible. The correlation, even when identified with a sufficient degree of significance, does not imply a deterministic causation. Functional *neuroimaging* data do not allow us to say whether the activation of an area is an epiphenomenon or is necessary for the elaboration of a thought or determines in a causal sense the performance of a task. This means that the visualization of brain areas and the identification of 'neural correlates' of certain mental states or actions do not allow to 'read minds' (to know whether a person is telling the truth or a lie) or to 'predict certain behaviours' (automatically linking intentional or unintentional behaviours), but rather only to predict them with a level of approximation that is not accurate. In this sense, the knowledge acquired and possible to be gained through new neurotechnological applications can not be used as 'certain data'.

The failure or malfunction of an important region of the brain decreases or may even completely prevent the corresponding function (e.g. language). In the case of neurological detection of 'defects in the instrument' (i.e. dysfunction of a region of the brain responsible for an important function) it is possible to attribute to the decreased or missing functionality of the region the impairment of the tasks assigned to it and possible consequential abnormal behaviour (or lack of behaviour). In this sense, functional brain imaging techniques, which are being introduced by courts, can lead to the request to recognize a reduced capacity to understand or want.

2. Bioethical problems

a) The reported studies (some of the most important and well-known) show how technological advancement have made it possible to greatly expand the research fields of neuroscience and to address issues of increasing complexity, in order to delineate new 'discipline' areas, such as for example, social neuroscience, within which the so-called 'Neuroeconomics' is becoming especially important. New *neuroimaging* techniques have led to an explosion of studies in the field of cognitive and psycho-social neuroscience[4]. In addition, the ease of reading and spectacular images have prompted a wider dissemination of the results of such research to a non-specialist public.

The application of neurotechnologies in these studies and research can stir up, due to the results and the information it provides, inevitable concerns with psychological consequences on the subject and family members. All this implies a necessary assessment of the reasons and purposes for such experiments.

[4] New perspectives could open, for example, in relation to functional magnetic resonance experiments that are proposed to probe brain activity, with particular attention to the possibility of communication in people with severe disorders of consciousness (e.g. those in a vegetative state, minimal conscience, *locked in*).

The ethical criteria of trials should also be applied in this area and approval of experiments should be given obligatorily within the scope of ethical committees. The *Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research* (2005) and, in particular, the *Explanatory Report* on the extension of biomedical research in all areas of intervention on human beings, not only in the biological sense but also psychologically, should be recalled[5]. The approval of experiments should be given provided that there is compliance with the precise and predetermined 'protocols' that bind researchers to respect certain limits[6]:

- the risk-benefit assessment with reference to the expected objectives, 'risks' are not to be understood only in a physical sense but also psycho-socially and 'benefits' can also mean it in a non direct and real sense (within the context of non-therapeutic research);
- free and informed consent - preceded by appropriate counselling - of those who undergo such investigations of the subject or guardian (with specific attention to those who are in a position of person and institutional vulnerability or relationship of dependency).
- the use of results, the balancing of the protection of *privacy* with the needs of society.

b) Even within the context of acquired data through these studies and research two types of problems arise.

1. First and foremost, the need for cognizant authorization by the subject regarding the use of information concerning him. Some applications of neuroscience, which lead to "the reading of the brain" bring into question confidentiality, also called 'brain *privacy*'. Consider the possibility that examination of the brain, originally aimed at obtaining certain information, ends up to providing other information that can be used to the detriment of the subject of the clinical trial (so-called *incidental findings*) or nevertheless prove risky in emotional or psychological terms. These are similar problems to those presented in the context of genetic testing.

There is also the ethical and juridical problem of the existence or nonexistence of an obligation to communicate the results to third persons, should they have an objective medical and social interest in the information. This is a question, once again, of the balancing of the individual right to *privacy* with other fundamental rights such as life and the health of other people who may be in jeopardy. In particular the right to confidentiality of "neurological information" may be outweighed by the need to protect the safety of family members with whom the person is in daily contact. Of course, this balancing can not be reduced to simply informing these third parties of the data, but information (as mentioned above) must be accompanied by proper counselling as to the meaning of the data, the psychological difficulties of the person - such

[5] Art. 2 (field of application): "for the purposes of this Protocol the term intervention include: 1. physical intervention, and 2. any other intervention in so far as this involves a risk to the mental health of the person concerned." The protocol stresses that any experiment on humans concerning his health, including mental, he must be approved by an ethics committee at the outset.

[6] The NBC has expressed its opinion on these issues in the documents: *Experimentation of new* drugs (17th November 1992); *Information and consent related to medical* acts, (20th June 1992).

as the obvious fears of abandonment or discrimination - which may have prevented a spontaneous communication to family members, and any measures to be taken, so that the information does not result in a mere shifting of responsibility, but into a tool to eliminate and reduce risks in general and, where possible and advisable to adapt family life to the new knowledge arising from knowledge of the information.

2. Another aspect of concern regarding the use of research results is constituted, in a general sense, by the impact of neuroscience on some traditional categories of philosophical thought that, today, can be investigated, at least in part, starting from the functions of the brain. There emerge, from these studies, 'theoretical and practical problems' that have/may have, especially in the medium and long term, a certain effect on the basic categories, behavioral models and practices, developed by social sciences and natural sciences.

Many of the findings of neuroscience link neuronal activity with thought and behaviour, producing new philosophical models for the understanding of man. Based on empirical evidence, there is a conceptual paradigm towards neurobiological reductionism and determinism. It is similar to what has already happened in genetic research, where reductionism and genetic determinism (the idea that human identity is reduced to the sum of genes and human behaviour explicable on the basis of genetic predisposition) have overshadowed other factors of a personal nature, as well as social-cultural-environmental nature that exert a key role in the genesis of states/mental dispositions and of behaviour. Therefore, on a philosophical level, there is in progress, a considerable debate on the' compatibility/incompatibility ' between new neurological data and subjective freedom/responsibility. It is a fundamental point that requires discussion, the NBC believes it essential that this be achieved in an interdisciplinary manner.

Regarding the implications of new neurological findings on the law and specifically on the cogency of legal rules, it must be said that the principle that the person in a mentally unsound state is not liable for illegal acts - precisely because he does not know or can not want – it has long been a part of our legal order as indeed in most of those of the West. It is a matter of comprehending whether the new diagnostic tools and neurologic assessment are recognized as reliable or not, according to the principle of eligibility/non eligibility of the incapable person. There have been multiple reflections and uses of neuroscience in the legal field in general and in particular in criminal law (eligibility of the subject in relation to free will; value of testimony, polygraph, sense of justice, etc.)[7]. The assumption is confirmed that the purpose of the law is to influence behaviour and educate, the users of legislation can not be separated from their ability to understand and use the rules as premises to guide their choices.

[7] In Italy cf. Judgement of the Court of Assizes of Appeal of Trieste on 18 September 2009. In the U.S., cf. the case *Perry v. Lynaugh* 1989, commented by A.Ş. Barth, *A double edged sword: the role of neuroimaging in federal capital sentencing,* in the "American Journal of Law and Medecine", 2007, vol. 33, No 2-3. For the purposes of the adjustment process to the scientific principles of criminal law decision, see also *Kumho Tire Co*. et al. *V. Carmichall et al*., 1999, commented in L. De Caldaldo Neuburg, *Neuroscienze e diritto penale. La scienza come, quando e perche'*, in "Neuroscience and the Law", edited by A. Santosuosso, Pavia 2009, p. 148 ff.

Recommendations

In the light of these emergent problems, the NBC makes the following recommendations.

1. Some studies in the field of neuroscience and neurotechnology could permit further knowledge and comprehension of the causes of human behavior giving the possibility to change and enrich the meaning of ethical, social and juridical responsibility. Neurotechnology can represent an interesting opportunity to give new contributions to the bioethical debate on the relationship between rationality and irrationality, between rationality and the emotional-sentimental dimension, as well as understanding of the ways in which decisions are made.

2. It is however fundamental to emphasize the importance of adopting a critical attitude as regards the results of these experiments which are often proposed to public opinion without adequate reflection as to the highlighting not only of the novelties, but at the same time also of the limits. The NBC makes reference to the responsibility of investigators and doctors and that of the media, which often emphasize uncritically acquired results, and calls for caution in communication of scientific data to the public, distinguishing correlation from the simple cause-effect relationship. Validation of the technologies used and constant revision of the hypotheses emerging from the results of experiments is required in order to avoid forms of discrimination in the social context. The call for caution is compulsory in the relationship between neuroscience and law, with particular reference to the assessment of accountability and reliability of testimony in court.

3. Considering the discovery of brain areas associated with the development of impulsive and violent conduct, it should be recognized that neuroscience can help to discover brain dysfunction that hinder the fulfillment of certain functions or that favour disturbed effects, in order to be able to suggest some treatments. Some scholars, for example, believe possible the early detection of those at risk and establish judgements of eligibility/non-eligibility on the basis of these criteria. Notwithstanding the problematic nature of these categories, in addition it is important, in theory, to draw attention to the fact that the neurological knowledge gained and acquirable through new technologies – despite the increase in our knowledge - can not constitute as such 'brain correspondence' of 'truth, freedom and responsibility", because such qualities are typical to 'people' and not to the 'brain'. The NBC intends to warn against a highly reductionist approach.

4. The studies and research in the neurological sector must still comply with the requirements of ethics inherent in any testing on human subjects, found in risk-benefit assessment, in informed consent and the authorization of the use of results, balancing the protection of '*privacy*' with the requirements of advances in knowledge and societal needs. A particularly important role is played by ethics committees that will have to acquire specific expertise in neuroscience. It is hoped that the scientific community will formulate codes of conduct, in order to ensure the growth of awareness and shared ethical behaviour.

5. The NBC calls for greater interdisciplinary comparison of the human sciences, especially philosophy as well as adequate and effective public debate – as is also repeatedly reiterated in the European and International documents aimed at national governments – for the promotion of knowledge and the

issues raised by the new developments in neuroscience in order to increase the understanding of citizens and further critical scientific information, that is objective and well founded.

Appendix - Neurotechnologies

Over the past thirty years, the advancement of methods of recording electrophysiological signals and the advent of new functional *neuroimaging* techniques have greatly expanded the possibilities for the study of complex cognitive functions. These include:

- electroencephalographic techniques (EEG) that directly record the electrical activity of the brain through electrodes placed on the scalp of the subject;
- the technique of the event-related potential (ERP) records with high temporal resolution the electrical activity related to the performing of specific perceptual, motor or cognitive tasks;
- magnetoencephalography (MEG) records the magnetic field associated with the electrical activity of neurons;
- magnetic resonance imaging (MRI) uses radio frequencies in the presence of magnetic fields;
- magnetic resonance spectroscopy (MRS) can detect changes in the metabolism of certain brain areas, for example in relation to the loss of neuronal function, recognizing the individual chemical compounds associated with the function / dysfunction;
- the *brain-computer interface* consents the reading of electroencephalographic signals, their correlation with the intentions of the subject and the translation of this correlation in commands for action**;**
- positron emission tomography (PET) allows the construction of a three-dimensional map of brain activity using the distribution of a radioisotope (e.g. in glucose), which is distributed in the brain areas that are activated in relation to a stimulus or also an emotional solicitation;
- functional magnetic resonance imaging (fMRI) allows the construction of a three-dimensional map, locating the areas activated by stimuli; generally contrast is provided by the call of blood flow in brain areas activated by a technique called BOLD (blood oxygenation level dependent); other approaches include the use of non-radioactive contrast agents;
- transcranial magnetic stimulation (TMS) consists in the application on the scalp of magnetic fields with certain parameters of intensity and frequency and permits to determine the behavioral effects of stimulation;
- the *brain fingerprint* measures brain waves when a piece of information is found lodged in the brain;
- the *multifaceted electroencephalographic response analysis* (MERA) measures brain waves that are formed in response to a sequence of words or figures/meaningful images that move rapidly on a monitor.