Comité
d'éthique
de l'Inserm

Ethical aspects of patients and professionals relationships

ERA-Net NEURON Cofund (Kick-off) meeting

Berlin 12th Jan 2016

Hervé Chneiweiss
Glial Plasticity and Brain Tumors
Neuroscience Paris Seine – IBPS
Cnrs – Inserm – UPMC
Paris France

Comité
d'éthique
de l'Inserm

Declaration of links of interest

President of the Ethic committee of Inserm
Member of the French National Ethic committee (CCNE)
Member of the International Committee for Bioethic of Unesco

I declare that I have no conflict of interest concerning the data contained in this presentation

Comité
d'éthique
de l'Inserm

Ethical aspects of biomedical research

Trois pôles de l'agir: "*ma liberté, ta liberté, la règle*"
Three dimensions of action: "my freedom, your freedom, the rule »

A l'affirmation par soi de la *liberté*, s'ajoute la volonté que la *liberté de l'autre* soit.
On the assertion of my own freedom, there is in addition the desire that the freedom of the other is.

Visée de la vie bonne, avec et pour les autres, dans des institutions justes.
Aiming good life, with and for others in just institutions.

Paul Ricoeur

Roots of ethics in modern biomedical research

4th century BCE, Hippocrates: "to help and do no harm" (*Epidemics*)

« Le principe de moralité médicale et chirurgicale consiste donc à ne jamais pratiquer sur un homme une expérience qui ne pourrait que lui être nuisible à un degré quelconque, bien que le résultat pût intéresser beaucoup la science, c'est-à-dire la santé des autres. » Introduction à la médecine expérimentale 1865 Claude Bernard (1813-1878)

"The principle of medical and surgical morality therefore is to never practice on a human being an experience that could only be harmful to her/him at any degree, although the result could be of great interest for science, that is to say the health of others. » Introduction to Experimental Medicine Claude Bernard 1865

1931 in Nuremberg Concept of informed consent

Comité
d'éthique
de l'Inserm

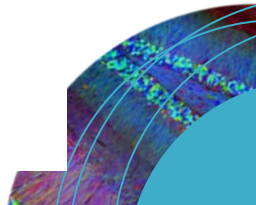
Roots of ethics in modern biomedical research (2)

1979 Tom Beauchamp and James Childress published the first edition of *Principles of Biomedical Ethics* (seventh edition 2013)

1979 The Belmont Report: guidelines for responsible research using human subjects

1. **Respect for Autonomy/ Informed consent**
2. **The Principle of Nonmaleficence**
3. **The Principle of Beneficence**
4. **The Principle of Justice**

Ethical issues raised by neurotechnologies are not necessarily unique or exceptional, **but the significance of the brain in human existence** generates powerful reasons both to intervene when function is damaged and to proceed with caution before intervening without good evidence of safety and benefit



A global challenge

There is an overwhelming need for treatments and interventions which can address diseases of the brain: WHO estimated the global cost of mental health conditions in 2010 at US$2.5 trillion, with the cost projected to rise to US$6.0 trillion by 2030.

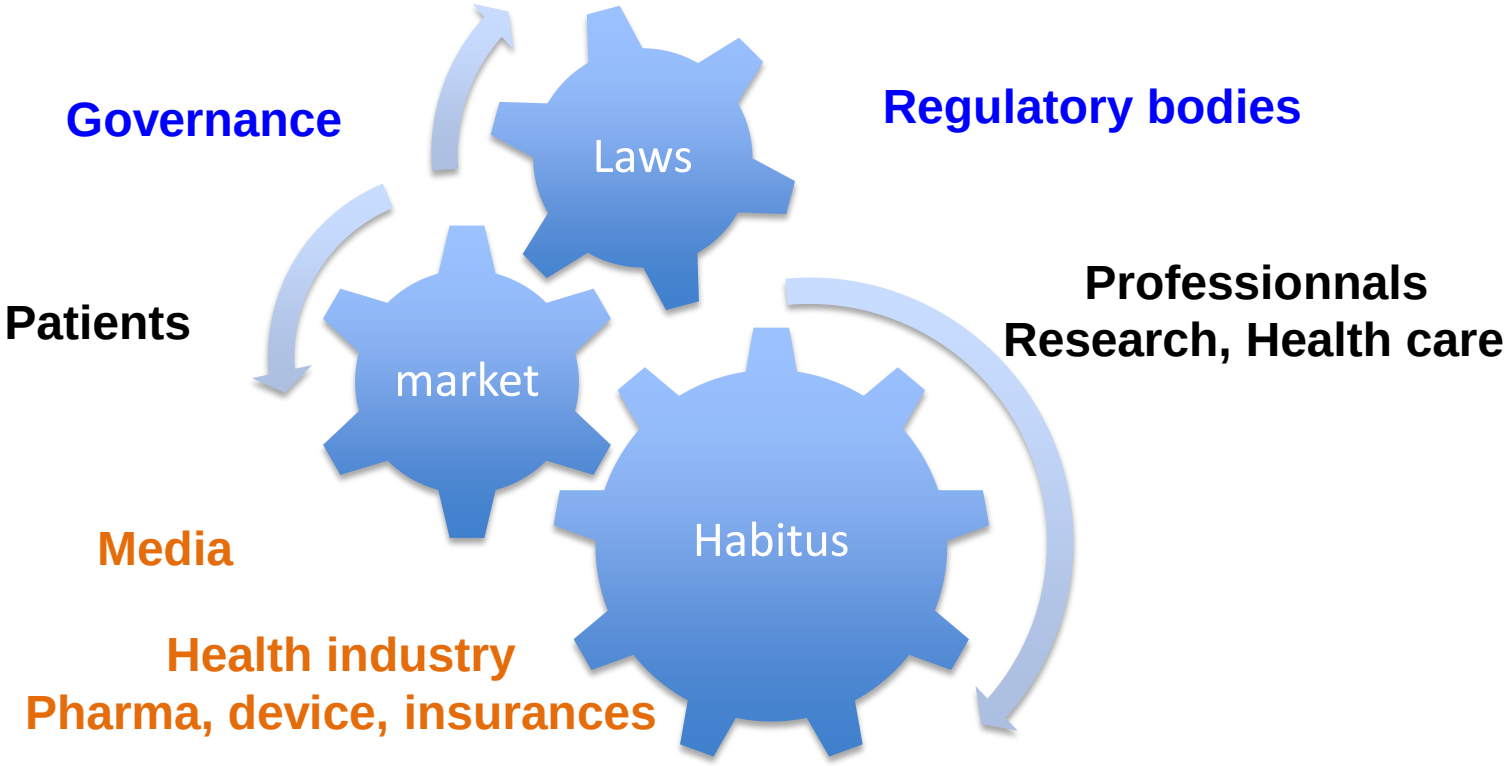
Ensuring public confidence in novel neurotechnologies will be crucial. This will require collaborative public engagement activities involving both researchers and clinicians, coupled with strong governance procedures and effective regulation.

A robust regulatory framework must be proportionate and based on a risk-benefit assessment to allow innovative research to demonstrate the safety and efficacy of new clinical treatments.

Taken from a Welcome Trust statement on the Nuffield Council report on Neurotechnologies 2012

Comité
d'éthique
de l'Inserm

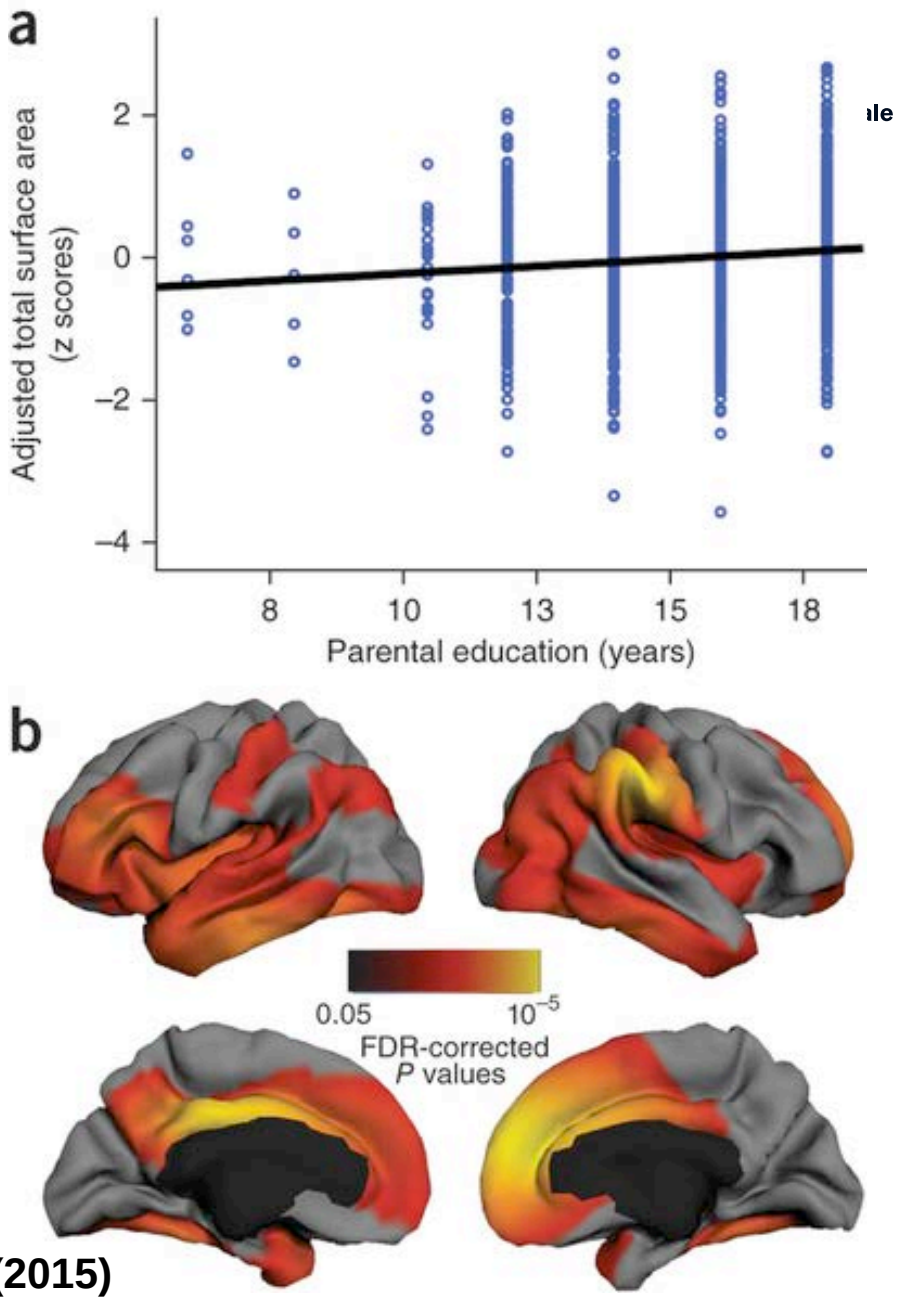
A global challenge (2): multiple stakeholders



Acknowledging that different stakeholders will have different views on what is good or valuable and what ought to be done

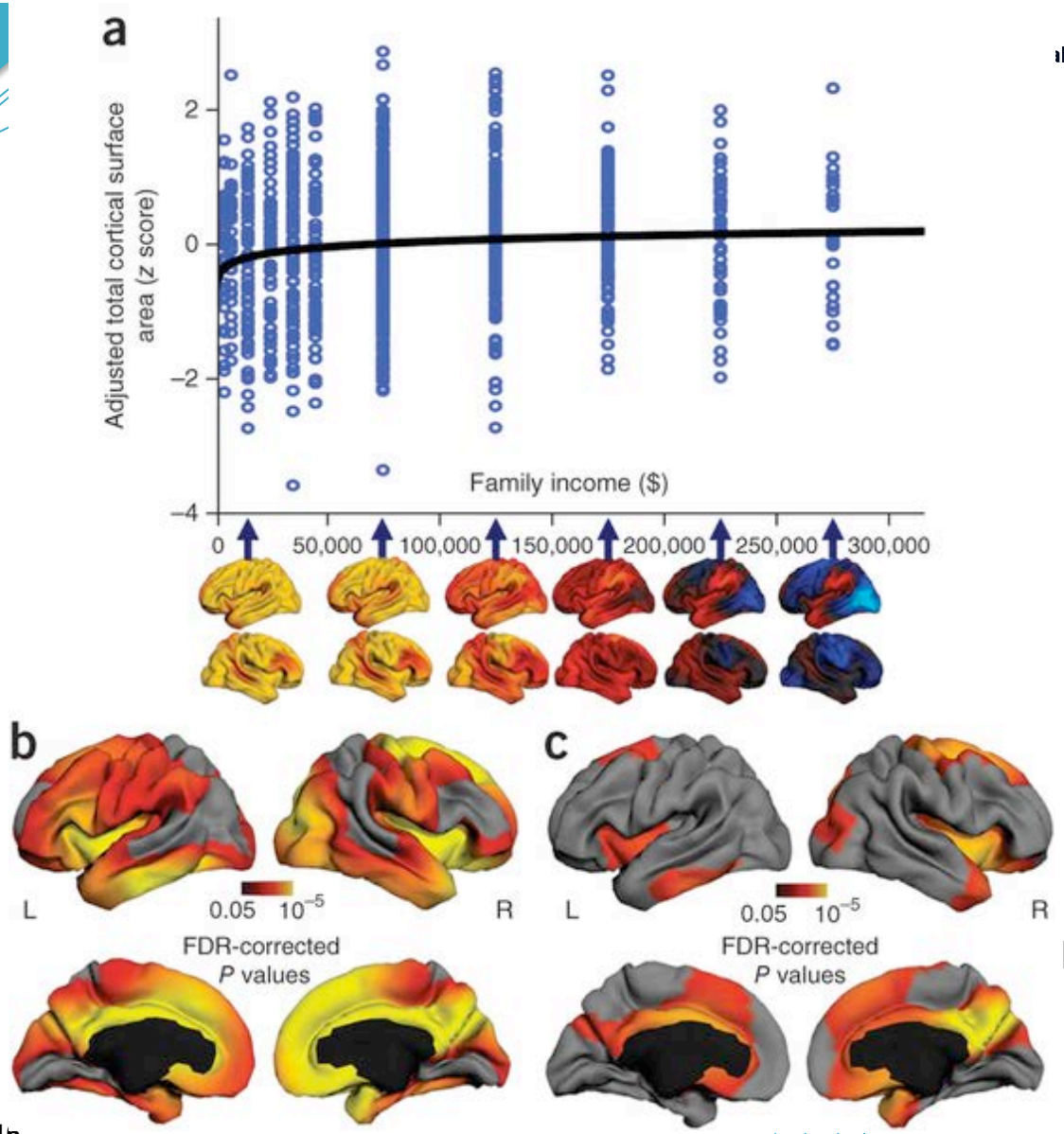
de l'Inserm

Parent education is linearly associated with cortical surface area (N = 1,099).



Noble et al.
Nature Neuroscience (2015)

Family income is logarithmically related to cortical surface area (*N* = 1,099).



Noble et al.
Nature Neuroscience (2015)

A challenge for autonomy

Informed consent in the Big Data era

Informed consent in predictive medicine:
genetic testing for Huntington,
pre-symptomatic biomarkers of Alzheimer's disease

Informed consent and incidental findings

Informed consent in the context of tissue donation/brain donation

Challenges for a real informed consent

Minimal criterias

1- **full details of the study must be delivered to the patient.**
This must include at least the nature, purpose, the course of the study, the risks and expected benefits;

2. **The patient must understand** this information and be able to make a decision (discernment);

3. The patient must be able to decide freely, without coercion, her/his potential inclusion in the study in a reasonable period of reflection. She/he may opt-out at any time.

Informed consent to a genetic test implies to know

1- the **nature of the information** resulting from the test that can be related to health and affect the livelihoods of people (eg sports or cognitive skills) or conversely have no connection with their lifestyle or health ;

2- the **probability of a phenotype** if a particular genotype is present;
the **concept of risk factor** should be clearly explained;

3- **the probability of when** a phenotype will emerge, such as the late onset of some health disorders;

4- **the severity** of the expected health disorder;

5- the possibility of **prevention or treatment,**

6- the **technical reliability and scientific validity** of the test.

Alzheimer's pathology: the amyloidosis path to neuritic plaques and the tauopathy path to neurofibrillary tangles.

Pathophysiological Changes

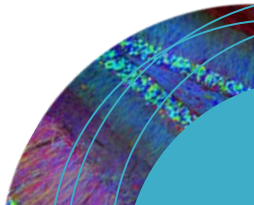
CSF measures of reduced concentrations of amyloid β, increased total tau, and increased phospho-tau, abnormal ratio of tau to amyloid β.

Are associated with very high rates of progression from amnestic mild cognitive impairment (MCI) to AD dementia and have shown a consistently high sensitivity and specificity in predictive models.

Cortical binding values for PiB-PET are predictive of cognitive decline and development of AD clinical signs in cognitively normal elderly individuals.

Topographical changes

Medial temporal lobe atrophy and reduced glucose metabolism in temporo-parietal regions on fluorodeoxyglucose PET predict the development of AD dementia in MCI cohorts



Do biomarkers make an AD?

Diagnosis can be uncoupled from a particular threshold of severity, and no need to anchor it to a dementia syndrome

Because individuals cognitively normal do have evidence of senile plaques and neurofibrillary tangles on autopsy, some of the people who have positive PET amyloid tracers will clearly not go on to develop cognitive impairment during their lifetimes.

Evolution toward AD might depend on genetic factors (eg, *APOE* genotype), other risk or protective factors (eg, vascular factors, diet, etc), and comorbidities (eg, diabetes).

These asymptomatic individuals with high risk of developing clinical symptoms would be candidates for preventive therapies, depending on the risk, expense, and side-effects of such therapies

Asymptomatic at-risk state for AD vs Presymptomatic AD

Ethical challenge

- What should mean the absence of an early diagnosis? The knowledge of a status is only valid at a presymptomatic or prodromal phase.

- Does the absence of a curative treatment of AD disqualify any early intervention? Secondary prevention including physic and intellectual exercice able to slow the pace of the disease seems to be more efficient if started early.

- Is it possible to set-up a care without a diagnosis and without revealing the diagnosis to the patient and her/his family?

- Is it possible to make an early care without discrimination of the affected individual related to the social vision of what means dementia?

- Challenge the basic « utilitarist » vision proposed by John Locke that we will be fundamentally unchanged in the future (our present self can reliably predict what will be best for our future self); What means « autonomy » facing a disease that will destroy this capacity of the affected individual.

The Principle of Nonmaleficence

- Toxicity
- Side effects
- Social consequences

- **Example of challenge for neuroscience: cognitive enhancement**

"augmentation cérébrale"	**augmentation**
"amélioration cérébrale"	**improvment**
"optimisation cérébrale"	**optimisation**
"dopage cérébral"	**doping**
"botox pour le cerveau"	**Cosmetology (botox for the brain)**

Means Increase that could be

Incremental	**linear or exponential**
Threshold	**Up or down**
U curve	

The Principle of Beneficence

Ex: Who should be enhanced?

on the one hand, modulation in the form of an increase of cerebral activity through biomedical techniques for patients affected by a neurological disease and/or deficit or handicap

on the other hand the use of such techniques by certain people whose health is in no way impaired.

As a result, the concept covered by this expression includes **the effects** induced by such modulation and also **the supposed intent** to enhance.

Neuroenhancement technics are poorly evaluated

Lack of consideration for negative effects, early or long term detrimentals

Paradoxical effect : enhancing one cognitive function to the detriment of another one for example, development of hyperamnesia but a deterioration of intelligence and social cognition?

The Principle of Justice

- Cost of access to treatment

- Availability of treatments

- Lack of good professionnal induces delay to diagnosis:
  - Autism and autistic spectrum
  - Rare diseases
  - Trouble of consciousness

- Discrimination/lack of consideration for particularities
  - People with deafness
  - dementia

New knowledge new challenge

- Some novel knowledge in neuroscience feeds public/media/politicians **imagination about possible brain manipulation**: Brain reading, subliminal images, trouble of consciousness..

- Some **novel practices may change our brain**: do screens modify the way we read or learn? Do microbiota impact our brain metabolism/ chronic inflammation/ neurodegeneration?

- Some **novel knowledge in neuroscience may change our approaches** to education, moral judgment, decision-making, but also obesity, diabetes…

- Consequently we have to face, and may be limit, **the « viral » « neuro » propagation** Neurolaw, neuroeconomy, neuromarketing, neuroeducation, **…**excepted for **neuroethics**

Feedback from the panel of experts of the 2015 ELSA in Neuroscience Call (Helsinki Oct 2015)

- Stronger integration of neuroscience with the ELSA disciplines would be beneficial, e.g. by including interdisciplinary ELSA teams directly into neuroscience projects.
  - The following complementary approach would be optimal: To open up “regular” NEURON calls for consortia with integrated ELSA teams and to open up ELSA calls for consortia with integrated neuroscience parts. Specific ELSA calls may remain.

- launch a Coordination and Support Action (CSA) to identify relevant topics and organise a call for these topics needed.

- it would be beneficial if even more countries would participate in upcoming calls.

- Future call topics should focus even more on global problems, in example: intellectual history or the interrelation between online security, biometrics and national defence, robotic assistance for elderly,

Comité
d'éthique
de l'Inserm

Harmonization of professionnal guidelines

Declaration of links of interest to prevent the conflicts of interest

Include an **ELSA work package** in cooperative research/consortia to promote ethical management of the data/material.
Example BrainNet Europe the brain banking network www.brainbank.nl

Open discussions for **improvement of informed consent** in the field of neuroscience and neurotechnologies.

Professional guidelines for **incidental findings** in neuroscience

Face controversies and promote scientific **integrity: i.e.** retracted publications should be rapidly removed of any data base and only the mention of retraction should remain

Engage discussions with the patients associations and more on the ethical management of neuroscience

Necessity to promote animal experimentation in the respect of the 3R but with the right model, namely primates for NDD, dogs for muscular dytrophies…

Open forum to the lay public within a scientific meeting. Example of Multiple sclerosis associations.

Synergies with organization sharing the same objectives such as the European Brain Council to identify the multiple decision-makers: politicians, but also finance and economy, regulatory agencies, philosophers,..

Comité d'éthique de l'Inserm

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

Pour tout contact avec le comité d'éthique de l'Inserm

Comite-ethique@inserm.fr

Thank you for your attention