Small treatise concerning the concepts of «invasivity» and «reversibility» and their relation to past, present and future techniques of neural imagery

Introduction

The aim of this text is threefold: Firstly, to prove to the Teacher that the author of this article (i.e. Student) have sufficiently internalized all the facts presented during UE Neuroimagery. Secondly, Student aims to introduce the notion of «invasivity» as something which should be considered wery seriously by someone who seeks an «ideal method» of conducting his future (neuro)scientific experiments towards success. But the ultimate aim si to show that certain «philosophical schools» who point out to «invasivity-related aspects» of current neuro-scientific research are not doing so from the position of moralizing savants locked in their ivory towers, but they do so because of concrete and highly-pragmatic reasons related to purest expressions of highest scientific practice.

Principal thesis of this text states that « invasivity » and « reversibility » aspects of a chosen experimental method should determine experimentator's choice at least as significantly as other aspects like spatial/temporal resolution characteristics, signal/noise ratio or economical feasibility.

First part of the text is dedicated to highly invasive techniques tissue extraction and analysis by means of electron, multiphoton or confocal microscopes. Post mortem autopsy and chirurgical interventions like vivisesction or lobotomy will be mentioned when discussing this group. Common demoninator of these approaches is that their *condition sine qua non* of their realisation is non-reversible and fatal degradation of one vital functions of the organism under study or...death.

Second part of the text is dedicated to somewhat more reversible, nonetheless still very brutal «in vivo» techniques like that of calcic imaging, optic imaging or electrode implantation. Because it is evident that such approaches can inflict severe injuries and suffering of the organisms under study, they will be labeled as «partially reversible quasi in vivo techniques».

Contrary to common categorisation of these days, even techniques like PET (positron emission tomography) or X-ray imaging will be included into this middle group of partially invasive techniques. This is due to their high-energy kinship with radioactivity which can without any doubt induce mutations resulting in the disequilibrium of a living system which is commonly known as «loss of health». The loss of this precious equilibrium is the reason why we'll include all the luminescence/fluorescence marker techniques into this category as well.

The third part of the text aims to bring hope. It will be fully devoted to techniques which can be considered as fully reversible: focus will be definitely on Magnetic Resonance Imaging (MRI) and Electroencephalography (EEG) while other non-invasive techniques (NIRS, echography or TCD) will be excluded from the list due to lack of Student's personal experience with these techniques. The small part of this final part will be dedicated to «what if?» speculation proposing to use these pure and elegant techniques not only for imaging, but as well as a tool of healing practice.

These three parts can be considered as a core of Student's homework demanding him to «*highlight the advantages and limits of these techniques depending from the scientific question You'll pose*». The question posed by student is this:

«According to what criteriae could we possibly quantify invasivity of an experimental tool or method ? »

This text will try to answer this question by introducing the term which we label hereby as «Information/Invasivity Quotient» (IIQ).We'll analyse this notion from more ethical perspective in Discussion section,while Appendix will summariz IIQ-based ranking of 4 presented methods.

1.Non-reversible techniques

Dans tout germe vivant, il y a une idée créatrice qui se développe et se manifeste par l'organisation.
Pendant toute sa durée l'être vivant reste sous l'influence de cette force vitale créatrice,
et la mort arrive lorsqu'elle ne peut plus se réaliser.

Claude Bernard, «prince of vivisectors»

1.1 Death

Death is a transformation of a system from living state into a non-living state. It is evident that the introduction of death into an experimental procedure leads to non-reversible lost of structure and hence its IIQ[1] should have value less than zero. Because of its essentially quallitative nature, it is very difficult, if not impossible, to quantify invasivity of such a transformation. One approach – strongly categoric one - could be to define its value as «minus infinity», but by introducing infinities into our quantification schema, we would de facto exclude and forbid the killing of an animal during the experimental procedure. We doubt that such an approach could be accepted by contemporain scientific community.

We propose somewhat more pragmatic and less categoric approach - introducing death into experimental procedure should decrease procedure's IIQ in an extent which is proportional to the complexity of the organism under study. Hence, for example, for procedures demanding « sacrifices » of complex animals like primates, IIQ should be -7, for other vertebrae it could be somewhere around -5 , -3 for insects, -1 for plants etc.[2]

Experimental techniques whose implementation implies death can be divided into:

Macroscopic: namely, a chirurgical in vivo procedure called vivisection. Aristotle introduced it, Gallieni made science out of it and western tradition perfected it. Application of this technique in physiology in general and in the domain of Neuroimagery in particular is today considered as obsolete.

Microscopic: when applied in the domain of biology, physiology and neurosciences in general, microscopes are devoted to the studies of tissues. This tissue is either extracted (c.f. Section 1.2 below) or studied in vivo (we'll refer to it partially in sections 2.1, 2.2) . In either cases, one has to first gain access to the tissue. Harm to the organism under study is often so severe that the only thing one can do with the animal after an experiment (if it does not die on its own) is to kill it. Since « **it** costs only 2 euros a piece» as we were told one of our teachers, approximately 50-100 million (Hendriksen, 2005) bodies of dead vertebra are annually being thrown into waste baskets of academic institutions.

When speaking about the role of death in experimental Neuroscience, one should not omit revolutionary works like (Broca, 1861) or (Wernicke, 1874). Since these were *post mortem* studies, i.e. the subject died of natural death, the role of death didn't decrease an IIQ of a given study. On the contrary, IIQ of these studies is highly positive since no suffering was caused and huge amount of new information/knowledge was obtained. It's possible that even in the forecoming century of nanotechnology, such post mortem studies possibly didn't say their last word. They could prove to be particularly fecond when combined with highly advanced **cryogenic methods.**

1.2Cuts

Death being the most drastic, it is definitely not the only transformation during which information or certain functional feature is irreversibly lost from the brain. Neurosurgical procedures like lobotomy or callotomy (disconnecting of cerebral hemispheres by cutting the

1 The basic axiom of Usability/Invasivity Quotient schema can be defined like this: An act which leads to loss of vital information decreases procedure's IIQ, while an act which generates new information (or even knowledge) increases procedure's IIQ. For more technical definition of what is information, see (Shannon & Weaver, 1949)

2 These numbers are more or less arbitrary and are subject to scientific discussion, we present them hereby just in order to clarify our « invasivity quantification » point.

central wiring of the brain - corpus callosum) left aside, we suggest that even procedures like skull penetration (SP) and tissue extraction (TE) of even a thin cortical layer are the acts of irreversible nature.

For the purpose of this homework, it has to be stated that **electron microscopy** cannot be done without preliminary TE procedure.

It can be argumented, of course, that plasticity of brain is very high and that this amazing organ is able to recover even from severe TE. If such is the case, one can ask why an animal is usually killed after TE-implying procedure. To reduce the number of such cases in the future, we propose to calculate the «Usefulness/Invasivity Quotient» of TE and SP by these example formulas:

$IIQ_{TE} = P_{TE}$ * (total amount of brain tissue / amount of tissue extracted)

$IIQ_{SP} = P_{SP}$ * (size of skull surface / skull surface which was damaged)

Where P_{TE} and P_{SP} are « tissue extraction penalization » and « skull penetration penalization » coefficients which should be, ideally, defined by ethical commitees independently for every specie « involved » in experimental studies.

Our highly arbitrary initial proposal is $-1 > P_{TE} > -3$ and $-1 > P_{SP} > -2$

2.Partially reversible «quasi in vivo» techniques

I quite agree that it is justifiable for real investigations on physiology; but not for mere damnable and detestable curiosity. It is a subject which makes me sick with horror, so I will not say another word about it, else I shall not sleep to-night.

Charles Darwin

2.1 Injections & Injuries

We hope that our method for invasivity quantification is getting more visible contours. It is now time to illustrate it on a concrete example.

A mouse is «constructed» in a way that the gene coding «luciferase» ensyme will get expressed when switched on by presence of oncogene and heat in the environement. When mouse is sufficiently ripe for being « sacrificied », tumor replication is than activated by an injected in the body, let's say in the brain area. Experiment then consists in applying heat on mouse's head, this will activate luciferase expression in tumor cells. Luciferase will catalyse production of luciferine, a photoluminescent substance (present in fireflies, for example) which will emit light and give to an experimentator an information about spatial distribution of tumors.

Such is often the philosophy behind «**optical imaging**» experiments. Highly sensitive CCD cameras incorporated into blackboxes which cost hundreds of thousands of euros will then produce a final result: a low resolution image from which it is evident that light (and therefore tumor cells) are present in the head of an animal. The discovery that « tumor cells are spreading from the area where experimentator had injected them » is indeed stunning and worth publishing - one can hope in obtention of new grants for new apparati[3].

Another example, this one from the domain of «**calcium imaging** »:

A bee is taken from its hive. She is fixed in the apparatus, anesthetized, top part of her « head » is removed. Dextran or acetylethylmester-like molecule is chosen from catalogue of Alexa or Oregon corporation, is bought and injected into upper layer of her central ganglion upon which **confocal microscope**'s laser is focalised. The « stimuli » is given after bee awakes from anesthesia.

Possibility to observe the calcium (and thus activation flow) in the cerebral networks is without any doubt a huge and non-negligeable advantage of calcium « imaging techniques ». It unites two important characteristics - it is microscopic and it is functional. In other words, spatial resolution is very high (depending from the microscope, it can go down to nanometers) and its temporal resolution is almost realtime. Nonetheless it has to be stated that the result of this technique is - - apart from invoice from Oregon or Alexa corporations - an image with few blinking pixel clusters supposedly containing non-generalizable information about functioning of a minute part of a ganglion of the unlucky bee dying slowly in horrible pains.

3 And it is evident that the presence of a new experimental apparatus has to be justified by new « sacrifices ».

It's evident that suffering about which we are speaking here cannot be quantified, cannot be transformed into numbers. But since it seems that men and women in white coats believe only in numbers, and since it seems to us that it is of utmost importance to change as soon as possible the habits of these men and women, we have to try, at least:

In addition to already proposed IIQ_{DEATH} , IIQ_{TE} and IIQ_{SP} factors, we propose these further criteria for quantification of invasivity and moral acceptability of an experimental method:

IIQ_{INJURY} - penalization due to injury. proportional to the time which the animal will need for complete recovery
$IIQ_{FIXATION}$ – penalization due to fixation of animal in the apparatus. relative to the means and proportional to the temporal length of fixation. Zero iff animal is studied in its natural niche
$IIQ_{BLEACHING}$ – penalization due to tissue bleaching by strong microscopes (confocal and multiphon)
$IIQ_{GENEMANIP}$ - penalization due to number and nature of genetic modifications (any additional modification makes the experiment more specific, artificial and hence less-generalizable and useful)
$IIQ_{ONCOINJECTION}$ – penalization due to tumor induction
IIQ_{TOXIC} - depends on the number and nature of substances classified as toxic which have been injected into animal because of the experiment
$IIQ_{NONTOXIC}$ – the same, but for nontoxic substances. **Includes fluorescence and luminescence markers**. The fact that they are considered non toxic (especially by the companies who produce them) doesn't mean that they don't have significant influence upon the overall equilibrium of the studied system and hence scientific significance of the results.

2.2 Isotopes & Implants

Methodes we mentioned in preceding parts were presented to students during their Neuroimagery course, and this is the reason why we have been mentioning them. They may seem interesting for biologists or chemists but not neccessarily so for cognitive scientists. Reason for this statement is the fact that (with exception of Broca&Wernicke's discoveries) no information about high-level functions (memory, attention, language, etc.) is obtained by applying of such methods.

On the contrary, the methods we shall discuss from this sentence on are of high interest for anybody whose interest doesn't stop at the level of tissue but goes further – towards mind itself.

The crudest approach how can one obtain information about high level functions of neural system is by means of **electrode implantation** into the brain. Since not much was told to the students about this approach, let it by said that introduction of such an approach should be penalized not only by IIQ_{TE} and IIQ_{SP} factors, but as well by a new factor $IIQ_{IMPLANTS}$ which should be proportional to number and size implanted sensors, as well as to the depth of implantation/invasion.

Much more subtle approach how one can observe the mysterious relations between mind and brain is by means of radioactivity**.** The most attractive approach is so-called **Positron Emission Tomograph** (PET) based upon the detection of gamma rays emitted by positron-emitting radionuclide tracer which was injected into the body. If the tracer is **fludeoxyglucose –** analogue of glucose – one can deduce the metabolic activity (glucose uptake) of different brain regions by simply observing the radiation (proportional to FDG concentration) of different regions.

From the invasivity point of view, one should take into account $IIQ_{RADIODECAY}$ factor proportional to half-lives of tracer's decay. In order to have such tracers, PET demands proximity of a nuclei-enriching cyclotron. Such a cyclotron can be possibly toxic to its environement.

PET is often coupled with a classical **X-ray CT scan.** Since CT scan uses also the high frequency electromagnetic waves as a medium for carrying the signal, $IIQ_{RADIOGAMMA}$ penalization -proportional to the energy level of a ray- should not be forgotten in its case.

Another disadvantage of CT is that fournishes only anatomic (and not functional) information. It stays, however, the most used apparatus in the clinical (neuro)imaging practice, which is definitely due to its relatively low price and high reliability.

3. Reversible techniques

L'exploration de l'esprit commence à peine, elle sera la principale tâche de l'ére qui s'ouvre devant nous comme l'exploration du globe a été celle des siècles précédents.

Thomas Huxley

3.1 Fields

From the point of view of cognitive sciences, the most attractive methods for the study of brain and mind are highly functional non-invasive methods of MRIf & EEG/MEG. All of them exploit, in certain sense, the «electromagnetic field»-related characteristics of human brain.

ElectroEncephaloGram (EEG) , discovered by Berger in 1924 exploits the fact that electric fields of activated cortical neurons -especially the pyramidal ones- sum up avec each other and produce an overall electric response which is measurable even on the outer surface of the skull. Hence invasion into the interior of the organism is not neccessary, electrodes are posed on the scalp and the only act of violence related to EEG measurement is due to movement-related artefacts – if organism moves , measurement is strongly perturbed. Hence the only negative factor of EEG is $IIQ_{FIXATION}$.

The negative factor of «unnatural fixation in the apparatus» is present as well during the experiments using **Magnetic Resonance Imagery** (MRI). MRI has two modes of functioning – anatomic and functional. Both exploit the properties of hydrogen protons who are susceptible two *align their spins* when exposed to powerful magnetic field. Subsequently, protons are being excited from this «equilibrium state» by strong radio waves. From the time-related distribution of emitted photons, one can subsequently reconstruct the overall map of matter in the skull. In case of functional MRI, a so-called BOLD effect is exploited as well – thanks to certain property of hemoglobine which is feromagnetic when oxygenized and paramagnetic when contrary is the case. Therefore one can be informed about blood flow in the region of interest (ROI). Since augmentation/diminution of blood flow in ROI is related to augmentation/diminution of neural activity in the proximity, MRIf gives us this very precious information.

The only other negative factor of MRIf is IIQ_{HEAT}, since it seems that longer exposition to MRIf device can lead to slight augmentation of body temperature. Since this is in order of approximately 1 degree Celsius, the IIQ_{HEAT} penalization is definitely lesser than in the «mouse-feet burning» experiments of optical imagery.

But in general it can be said that EEG as well MRI are definitely positive approaches when analysed through the prism of «Invasivity/Information Quotient» schema. This is due to huge «information contribution » factor, i.e. due to the fact that *these apparati produce huge amount of information*. To calculate «information contribution» one should take into account these factors: 1) R_S - Spatial resolution (voxels per skull volume or electrodes per skull volume) , 2) R_T - Temporal Resolution and 3) SN - Signal/Noise ratio 4) T – overall Timelength of datacapture 5) I – sensor sensitivity, i.e. numbers of degrees of freedom of individual sensor (for example number of possible intensity values in the case of a CCD pixel)

The output of a simple formula

$$IIQ_{INFOCONTRIB} = R_S * R_T * SN * T * I$$

is a hypotethic overall amount of pure information (purified signal) obtained during experiment.

As we already stated, this $IIQ_{INFOCONTRIB}$ component is very high in case of EEG and IMRf. In the former case it is due to very high R_T (dataset size obtained from one experiment is in order of Megabytes) while in case of the latter , it is due to very high S_T (dataset size obtained from one experiment is in order of hundreds of Megabytes, even Gigabytes). By subsequent logarithmization of these information contribution quantities (for example log10(Megabyte)~6; log10(Gigabyte)~9) one gets numbers which can be more easily used of in the final IIQ equation (c.f.Appendix)

3.2 Life

Since students weren't introduced to other non-invasive methods like **MagnetoEncephaloGram** (MEG), **Near-Infrared Spectroscop**y (NIRS) , **Transcranial Doppler** (TCD) or simple **ultrasound** imaging , we'll not concentrate upon these methods on this article.

Upon what we will concentrate in this concluding paragraph is this set of hypotheses:

It is obvious that brain is electromagnetic-field generating device. Many indices suggest as well that brain is susceptible to EM-field stimulation. It may be, thus, that the brain sustains its internal equilibrium by means of its own EM-field (skull functions as resonator, glium cells as amplifiers) How comes that modern science is completely blind to the power of field-based techniques and stay obsessed by its poisonous molecules, pillules and deadly rays ?

After his first experience of meditation in 3-Tesla MRI in Bordeaux, Student is deeply persuaded that these most sophisticated devices ever created by humanity[4] can be used not only for imagery, but for healing as well.

For burning the tumor in much more subtle way than an X-ray could ever do.

Discussion

> *Il devient indispensable que l'humanité formule un nouveau mode de penser*
> *si elle veut survivre et atteindre un plan plus élevé.*
>
> Albert Einstein

. This text is written by student of Practical School of High Studies. Maybe the term «High Studies» are interpred in a bad manner by the Student , nonetheless his conscience obliges him to state that he believes that the ultimate goal of his studies is *scientia*, and we know for ages already that true scientia reposes on discovery of general principles.

More general the principles, higher the science.

This text is written by a young man who got, in certain moment in his life, into contact with so-called «oriental» philosophy and science. The foremost ethical principle of eastern thought can be stated like:

«There exist a causal cause-effect relation not only on material, but as well an axiological – i.e. moral - level».

This principle is known as «the law of Karma» in the East. Western tradition knew it as well: «As You saw, so shall You reap» was said thousand years ago, and was later translated into a Golden Rule before finally finding its most general form in Categoric Imperative (Kant, 1785).

But even Kant made a mistake: he excluded animals from implementation of this principle.

This text is written a cognitive science student aiming to program an Artificial Intelligence (A.I.) system. Since it is not a secret that an ultimate goal of a Robotics & A.I. research is an emergence of a thinking and acting entity whose skills will be superior to that of a human being we appeal to all those men and women of scientia who have ears to hear and eyes to see:

<u>If You will not reconsider Your practices immediately[5], You will not be able to exclude the possibility that the future superiors will do to You the same thing as You did to Your inferiors.</u>

To conclude: We state hereby that IF the principle of Karma is true (and we suggest that whole human history did not falsify it), an experimental method which does not take it into account is doomed to fail since *ex vi termini, one cannt heal cancer by injecting cancer into healthy beings*.

To conclude: The law of Karma states that You simply cannot have good scientific results if Your method for achieving them is not good neither.

To conclude: if we were «moralizing», we truly did it out of pragmatic concerns.

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4 Nothing excludes, in theory, to exploit MRI devices like macroscopic quantum computation machines, but to analyse this in this article would bring us too far away.

5 Shubhasya shiighram ashubhasya kálaharaṅam (Do virtue immediately, delay doing vice)

Appendix – Towards concrete implementation of Information/Invasivity Quotient

L'esprit occidental est dans le vrai seulement par ses méthodes et ses techniques.
L'esprit oriental est dans le vrai seulement dans ses tendances générales.
L'échange est nécessaire.

Georges I. Gurdijeff

Our «Invasivity/Information Quotient» proposal for the estimation is simple:
On one side of the equation we put all the «invasivity» related factors – quantified and weighted according to common international conventions.
We label the resulting sum of all the quantified invasivity factors $IIQ_{NEGATIVES}$ i.e.

$$IIQ_{NEGATIVES} = IQ_{DEATH} + IIQ_{TE} + IIQ_{SP} + IIQ_{INJURY} + IIQ_{FIXATION} + IIQ_{BLEACHING} + IIQ_{GENEMANIP} + \\ + IIQ_{TOXIC} + IIQ_{NONTOXIC} + IIQ_{RADIODECAY} + IIQ_{RADIOGAMMA} + IIQ_{HEAT}$$

On the other side of the equation we put the weighted $IIQ_{POSITIVES}$ factor. Since it gives us pure information content in bits, we weight it by means of logarithm function to make it comparable with $IIQ_{NEGATIVES}$

$$IIQ_{POSITIVES} = \log(IIQ_{INFOCONTRIB})$$

The basic imperative of Information/Invasivity Quotient heuristics states that if

$$IIQ_{POSITIVES} - IIQ_{NEGATIVES} < 0$$

than the amount of pure signal (information) generated by an experiment is not sufficient to justify the harm caused to an organism and therefore such an experiment should not be peformed.

Very naive (and somewhat arbitrary) illustration of our point is present in following table representing negative and positive aspects of an experiment lasting approximately 1 hour :

	List $IIQ_{NEGATIVES}$	N of $IIQ_{NEGATIVES}$	$IIQ_{POSITIVES}$ log10(IIQinfocontrib)	$IIQ_{POSITIVES} - IIQ_{NEGATIVES}$	Decision
Optical in vivo	IIQ_{INJURY}+IIQ_{HEAT}+$IIQ_{NONTOXIC}$ + $IIQ_{GENEMANIP}$ + IIQ_{TOXIC} + $IIQ_{ONCOINJECTION}$+ ???IIQ_{DEATH}	7	3	< 0	reject
EEG	$IIQ_{FIXATION}$	1	6	> 0	accept
MRI	$IIQ_{FIXATION}$, IIQ_{HEAT}	2	7	> 0	accept
NIRS	none	0	5	> 0	accept

Bibliography

Trouver d'abord.
Chercher après.

Jean Cocteau

Broca, P. (1861). Remarques sur le siege de la faculté du langage articulé, suivies d'une observation d'aphemie (Perte de la Parole). *Bulletin de la Société Anatomique*, *6*, 330–357.

Hendriksen, C. F. M. (2005). The ethics of research involving animals: a review of the Nuffield Council on Bioethics report from a three Rs perspective. *Alternatives to Laboratory Animals: ATLA*, *33*(6), 659-662.

Kant, I. (1785). Groundwork of the Metaphysic of Morals. *First published*.

Shannon, C. E., & Weaver, W. (1949). The mathematical theory of information. *University of Illinois Press*, *97*.