Functional Magnetic Resonance Imaging

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Functional Magnetic Resonance Imaging

Understanding the technique and addressing its ethical concerns with a future perspective

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Members of the Working Party

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"With the fMRI results in the very early nineties, MRI itself took on an entirely new direction. Rather than MRI providing only anatomic and some basic physiologic information, it now could produce dynamic brain activation maps quickly, non-invasively, and with relatively high resolution. Many MRI technicians, industry engineers, marketing people, radiologists, scientists and others of the MRI establishment were nonplussed as researchers started having healthy volunteers, in the name of brain activation, doing all kinds of odd things in the magnet other than simply lying perfectly still with eyes closed — then producing highly processed and wildly colored maps rather than the standard gray scale. A revolution had begun. We could now look into the human brain as never before — and we were leveraging mostly established technology to do it."

Peter A. Bandettini, fMRI pioneer, 2012

Foreword

Functional magnetic resonance imaging (fMRI) has revolutionized the study of the human brain functions *in vivo*. Due to the rapid implementation, particularly in neuroscience research, and complexity of this imaging method, its development and use has not been always adequately supported by ethics. It was the aim of this document to provide a reflective assessment of the ethical issues that are raised by fMRI and propose solutions, not separating this assessment from a sound background on the history, functioning, limits, safety, applications and future of the technology.

Daniela Seixas
Chair of the Working Party

Objectives

To explain the functioning, risks and limits of the technique of functional magnetic resonance imaging (fMRI), in the context of its history and future perspectives.

To identify and consider the ethical issues that arise from the use of fMRI to study the human brain in clinical practice and in research, and in non-medical and non-research settings.

To produce recommendations on ethics useful for research, policy, governance and public engagement.

Abbreviation List

ACR – American College of Radiology

AD – Alzheimer's disease

ADNI – Alzheimer's Disease Neuroimaging Initiative

BOLD – blood oxygenation level dependent contrast

CPT – current procedural terminology

DBS – deep brain stimulation

DMN – default mode network

EEG – electroencephalography

FDA – U.S. Food and Drug Administration

fMRI – functional magnetic resonance imaging

FMRIB – Oxford Centre for Functional Magnetic Resonance Imaging of the Brain

IF – incidental findings

MEG – magnetoencephalography

MRI – magnetic resonance imaging

NMR – nuclear magnetic resonance

PET – positron emission tomography

phMRI – pharmacologic MRI

RF – radiofrequency

SAR – specific absorption rate

SMF – static magnetic field

SPECT – single-photon emission computed tomography

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Part One

Introduction

Introduction

The brain is the most complex organ in humans and is responsible for controlling the body. Since time immemorial, it has been an object of fascination. Although the brain is related to the mind, still today the mechanisms by which it gives rise to thought and consciousness are not completely understood.
Magnetic resonance imaging (MRI) is a non-invasive and relatively safe imaging method that allows the visualization of the structure and many of the pathologies of the human brain in vivo, and that more recently is able to study the brain functions. MRI came into clinical use in the early 1980s, a few years before the first successful functional magnetic resonance imaging (fMRI) experiment in 1991 (Bandettini, 2012).

The availability of MRI scanners has increased rapidly in most European countries over the past two decades (OECD, 2012). For example in the Netherlands, the number of MRI units *per capita* increased tenfold between 1990 and 2010 (OECD, 2012). Similarly, in Italy, the number of MRI scanners *per capita* increased by nearly six times between 1997 and 2010 (OECD, 2012). The success of fMRI is believed to be a result of the good accessibility to MRI scanners, the parallel development of computing power and the advances on brain physiology and MRI signal knowledge (Bandettini, 2012).

1.1 Historical perspective

The phenomenon of nuclear magnetic resonance (NMR) was intensively investigated in the twentieth century. NMR in a solid was first described in 1946 by the research teams of Felix Bloch and Edward Purcell, together awarded the Nobel Prize for physics in 1952. They explained that if a group of atoms whose nuclei have a magnetic moment (the force that a magnet can exert on electric currents and the torque that a magnetic field will exert on it) is placed in a magnetic field, their nuclei can be regarded as magnetic dipoles precessing (changing the orientation of their rotational axis) about this field at a certain frequency, which is defined by the multiple of a constant that is unique to those atoms and the magnitude of the field. If these dipoles (closed circulations of electric current) are simultaneously affected by an electromagnetic radiofrequency (RF) field of a frequency matching in resonance that of their precession, they will interact

with that field. Physically, this means that these nuclei will absorb energy from the RF field and change their nuclear state. These fundamental principles together with other technical and analytical developments led to modern MRI. Paul Lauterbur, working in the United States, conceived a technique to noninvasively map NMR differences in different tissues of the body (Lauterbur, 1986), and Peter Mansfield, working in the United Kingdom, developed a mathematical process to obtain MRI images in less than one second (Mansfield and Maudsley, 1977), making blood oxygenation measurement possible in humans as explained below. For their contributions they were jointly awarded the 2003 Nobel Prize in Physiology or Medicine.

Functional MRI is an MRI technique little more than twenty years old, based as well on the behaviour of biological tissues under the influence of magnetic fields, but relying specifically on an NMR method for measuring blood oxygenation. Linus Pauling reported already in 1936 that the magnetic susceptibility of blood haemoglobin (iron-containing protein for oxygen transport found in the red blood cells) changed as a function of whether it was bound to oxygen or not (Pauling and Coryell, 1936). In 1990, the extravascular effect of intravascular blood was described in the brains of rats at the high field of 7 T (tesla is a unit of magnetic field strength), and the term blood oxygenation level dependent contrast (BOLD) entered the fMRI lexicon (Ogawa et al, 1990a; Ogawa et al, 1990b). BOLD is the process of oxygenation by which oxygen is reversibly bound to the ferrous ion of haemoglobin in red blood cells; Ogawa sagaciously hypothesized that the BOLD effect was related to functional states of the brain (Ogawa et al, 1990a; Ogawa et al, 1990b).

Although the first successful fMRI experiment, which studied brain visual areas in 1991, did not use the BOLD effect (but an exogenous source of contrast, not haemoglobin), it heralded the beginning of the use of MRI to map human brain functions (Belliveau et al, 1991). The application of the BOLD technique to human neuroimaging was soon reported by others (Bandettini et al, 1992; Kwong et al, 1992; Ogawa et al, 1992). It deserves mention that positron emission tomography (PET) studies contributed to the understanding of the BOLD effect. Fox and colleagues, using PET, described that with brain activation, oxygen extraction decreased, implying an increase in blood oxygenation, predicting that the BOLD signal should increase with activation (Fox and Raichle, 1986).

Since the early 1990s, the advances in fMRI have consisted of developments in hardware, imaging methods, image processing and display software, and paradigm design (manner of stimulating the brain in order to obtain meaningful information). These methods and technologies are still evolving, as fMRI users demand increasingly more spatial and temporal resolution, specificity, sensitivity and robustness (Bandettini, 2012).

1.2 Understanding fMRI

Using a static magnetic field (SMF) that typically ranges from 0.5 T to 3 T (3 T is about 50,000 times greater than the magnetic field of the Earth), and much weaker varying magnetic fields, MRI makes use of the NMR phenomenon. MRI, conventionally used to reveal the structure of an anatomic region of interest, exploits the magnetic properties displayed by the atomic nuclei of the molecules of the human body, particularly hydrogen because of its abundance in the water and fat of the tissues.

Functional MRI also takes advantage of the magnetic properties of the biological molecules, in this case, haemoglobin. The different magnetic susceptibilities of haemoglobin in its different oxygenation states explains the mechanism that underlies BOLD contrast used in fMRI (Thulborn, 2012). When we speak, move or think (and when we are even at rest) certain areas of our brains become involved in these tasks. The neurons involved in the process demand more energy locally, consequently increasing regional blood flow and, relatively, the amount of oxyhaemoglobin (magnetically more inactive than deoxyhaemoglobin), which in turn locally increases the MRI signal. By structurally sampling the brain every few seconds, fMRI is able to provide temporal data of the MRI signal in each image voxel (or volume-pixel, the smallest distinguishable cube-shaped part of a three-dimensional image).

Functional MRI may have slightly lower spatial resolution than anatomical MRI because a sample of the whole brain is needed every few seconds (while a conventional structural scan takes minutes to acquire), but is better than other techniques that study brain function, such as PET or electroencephalography (EEG). On the other hand, because of the nature of the method (dependent on blood flow to indirectly measure neural activity) and of the time needed to sample the whole brain, fMRI has lower temporal resolution than techniques that directly measure the electrical activity of the brain, namely EEG or magnetoencephalography (MEG). Other fMRI techniques were

developed (Williams et al, 1992), but are not widely used because they are generally limited in sensitivity, brain coverage and temporal resolution relative to BOLD contrast approaches (Bandettini, 2012).

To illustrate the technique, an example of a simple fMRI study with a motor task is given. After a safety screening for entering the strong magnetic field of the MRI scanner, the subject lies inside the magnet tunnel during the functional scan, while alternating 30-second periods of opening and closing movements of the hand with rest. A second structural MRI sequence of high spatial resolution of the brain is also obtained for image registration purposes (functional and anatomical image alignment). Although depending on the task and the purpose of the scan (clinical or research), most studies can be completed within approximately 20 to 40 minutes. Complex image processing is then needed to detect the activity in each brain image voxel and is defined as how closely the time-course of the MRI signal from each voxel matches the expected time-course (the alternating 30-second periods). Voxels whose signals correspond are given a high activation score, voxels showing no correlation have a low score and voxels showing deactivation are given a negative score. These can then be translated into activation maps that are, in fact, statistical maps that may represent for example a t-test, or in other cases, an ANOVA or a non-parametric statistical test.

In the fMRI field, a task paradigm is the manner (timing, duration and magnitude) in which a stimulus is presented to the subject being scanned in order to activate certain brain regions. The stimulus used depends on which brain functions need to be studied, and may be for example motor (as illustrated above), sensorial, language or cognitive. The most commonly used paradigm designs are block design and event-related design (Figure 1).

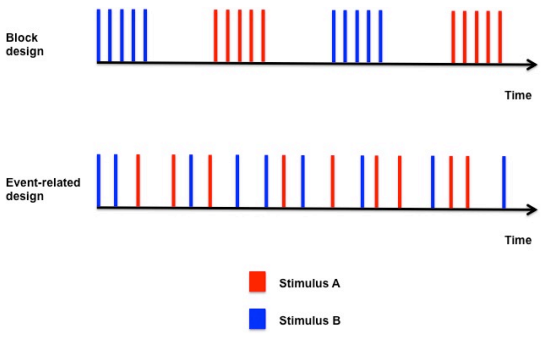

Figure 1. Common fMRI paradigm designs: block and event-related.

Block design was adapted from PET experiments that had lower temporal resolution; it usually consists of alternating periods of 20-30 seconds of two (sometimes three) conditions, for example stimulus and rest, to determine the differences between these conditions. In *event-related* fMRI, on the other hand, the presentation of the individual stimuli usually lasts only a few seconds, is randomized and the time between the stimuli can vary (Buckner et al, 1996). This technique is ideal for cognitive tasks, attempting to model the change in MRI signal in response to neural events associated with behavioural trials. A *mixed* block design and event-related approach is also possible (Visscher et al, 2003).

An innovation in paradigm design (Spiers and Maguire, 2007) that is re-emerging is the *free-behaviour* design, closer to the real world, yet still amenable to experimental control (Maguire, 2012). Non-constrained paradigms have been important in memory research (Cabeza and St Jacques, 2007). An example of free-behaviour design for the study of memory would be to show participants short film clips before scanning and then asking them to recall the clips during the fMRI session (Maguire, 2012).

Resting state fMRI is a paradigm design in that there is no external input to induce brain activity. It relies on spontaneous ongoing brain activity that translates in signal fluctuations that are correlated between functionally related brain structures (Figure 2). Although now it is an established methodology, much of the early research work was dedicated to demonstrating that the effect was neuronally based and functional in nature and did not correspond to noise of the MRI data (Lowe, 2012).

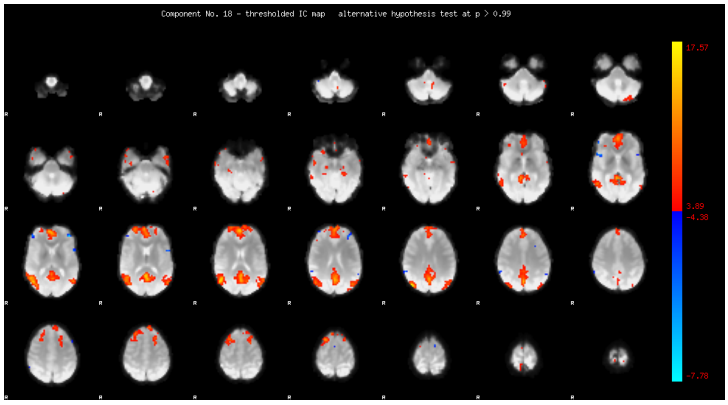

Figure 2. Default-mode network (DMN) brain map obtained with resting fMRI (it does not use a task to investigate brain functions). The DMN deactivates during demanding cognitive tasks and is involved in internal modes of cognition; it seems to be important in planning the future and in social interactions. Maps of other neural networks functionally connected during rest may be collected, for example sensory-motor, visual and auditory networks.

Real-time fMRI allows immediate access to functional brain imaging results by allowing the analysis of data as they are being acquired. This almost immediate availability of results is useful for quality control or fast functional localization (Weiskopf, 2012), which may be important for example in studies for presurgical planning of brain lesions in non-cooperative patients. Real-time fMRI has been used as a brain-computer interface for neurofeedback, to train self-regulation of the local BOLD response and to study consequential behavioural effects such as modulation of pain, reaction time, linguistic or emotional processing (Weiskopf, 2012).

1.3 Limits of the technique

Several limitations of fMRI have been identified, and include limitations associated with the neurovascular coupling phenomenon, the experimental design, reliability and validity of paradigms, head motion, physiological noise, structural changes in the brain, image registration, spatial and temporal resolution, field strength, image statistics (false positives and false negatives, correction for multiple comparisons, power calculation, sample size, region-of-interest analysis, inferences to the population), influence of cultural and anthropological frameworks in data interpretation, hardware and software diversity, and lack of normative procedures (Logothetis, 2008; Seixas and Ayres-Basto, 2008; Seixas and Lima, 2011). Many of these issues converge in fundamental questions concerning the interpretation of fMRI data, and conclusions drawn from results often ignore the actual limitations of the method, including those imposed by the particular circuitry and functional organization of the brain (Logothetis, 2008).

Robert Savoy, reflecting on the fMRI education for researchers, states that data interpretation is the most challenging aspect, and requires a long apprenticeship and extensive practice of data analysis (Savoy, 2012). Moreover, fMRI veterans recognize that expertise in fMRI requires knowledge in a wide array of domains and that training programs have to deal with the challenge of teaching researchers from a variety of backgrounds. This situation is now changing, with most researchers having previous fMRI experience (Savoy, 2012). In Europe, the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB, http://www.fmrib.ox.ac.uk/) and the Wellcome Trust Centre for Neuroimaging of the University College London (http://www.fil.ion.ucl.ac.uk/) are multi-disciplinary neuroimaging research facilities,

which focus on the use of MRI for neuroscience research, brain imaging data analysis software development and fMRI education.
There are new educational challenges, related to the growing list of technologies now used to study human brain function in combination with fMRI (for example EEG, taking advantage of its high temporal resolution). Another overwhelming challenge is that of educating consumers of fMRI claims as the technique becomes more influential in society (Savoy, 2012).

In spite of the complexity of the technique, as seen before, and its relative newness, a lot appears to already have been done in trying to further understand its physiological mechanisms and its limitations, particularly with respect to MRI sequence development, experimental design and image processing methods and statistics (Bandettini, 2012). Taking the example of resting state fMRI, nearly 10 years passed before the controversy about its meaning and interpretation subsided in the specialized literature and it was accepted as a valid scientific method to study the functional connectivity of the brain (Biswal et al, 1995; Lowe, 2012). As a recent article celebrating the 20 years of fMRI stated,

> "In the past twenty years there has existed a dynamic tension between those moments when we have been stunned by what fMRI has revealed and those moments when we have been cautioned of real or perceived fMRI limits or problems. While of absolute limits exist with regard to imaging technology, sensitivity, resolution, and how much we can actually infer about neuronal activity from the haemodynamic response, I don't think that we will truly bump up against them any time soon. At this point in time, I think that the community is still well within the steep part of the learning curve with regard to figuring out how best to extract, use, and interpret the fMRI signal" (Bandettini, 2012).

1.4 Safety issues

The risks of an fMRI scan do not differ much from those of a conventional MRI exam, with the possible exception of eventual risks or discomfort for the subject related to stimulus presentation. Also, in longer fMRI acquisitions and due to certain type of sequences commonly used, or at ultra-high magnetic fields, the discomfort related to

time-varying field and the SMF may be more noticeable, as explained below. In a study quantifying adverse events associated with fMRI and real-time MRI, 641 imaging scans of 114 patients participating in a clinical trial were not associated with an increase in adverse event number or severity (Hawkinson et al, 2012).

Patients and volunteers undergoing MRI examinations are exposed to SMF and time-varying magnetic fields (gradient fields and RF fields):

1.4.1 Static magnetic field

The biological effects most likely to occur in patients and volunteers undergoing MRI procedures are vertigo-like transient symptoms, particularly induced by movement in the strong SMF of the MRI scanner. Moving patients slowly into the magnet tunnel may avoid these sensations. In addition, the accumulated experience of MRI procedures in clinical situations, where exposures to fields of 3 T are becoming increasingly common, does not suggest that any obvious detrimental field-related effects occur, especially in the short term (Health Protection Agency, 2008).

Much less is known about the effects of the ultra-high field MRI scanners, with a magnetic field strength of more or equal to 7 T. According to current knowledge, it is not expected that exposure of human subjects to magnetic fields of this magnitude implies specific risks, provided that known contraindications to MRI are observed (Moller and von Cramon, 2008). However, transient phenomena such as vertigo, nausea, metallic taste or flashes of light are more frequently observed comparing to weaker magnetic fields of 1.5 T (Heilmaier et al, 2011; Moller and von Cramon, 2008).

Similarly, little is known about the effects of SMFs on growth and behavioural development of fetuses and infants, suggesting caution is warranted concerning their imaging (Health Protection Agency, 2008). Kok and colleagues looked at 35 children who were exposed to a field of 1.5 T during MRI exams in the third trimester of pregnancy, and found no adverse effects on eye or ear functions, or on reproductive outcome (Kok et al, 2004). Of notice is the emerging field of fetal fMRI, with the potential to provide insight into early brain function (Schopf et al, 2012).

Regarding potential long-term effects of MRI, the overall evidence from epidemiological studies does not suggest adverse health effects from exposure to SMFs; however,

evidence is limited (Health Protection Agency, 2008). Additionally, there are no published studies of mortality or cancer incidence among subjects undergoing MRI procedures (Health Protection Agency, 2008).

There is also risk of displacement, vibration or damage of electronic or electronically conductive implants or metals, especially those containing ferromagnetic matter, under the SMFs, and in general MRI exams are contraindicated for patients with such materials. Because of the importance for clinical medicine of MRI, more and more medical devices nowadays are being produced to be MRI compatible. The Journal of the American Medical Association reported the first MRI-safe pacemaker to receive conditional approval from U.S. Food and Drug Administration (FDA) in 2011 (Mitka, 2011). All persons to enter an MRI scanner room, including patients, healthy volunteers and staff must be screened for implants or metals and other potential safety concerns (Expert Panel on MR Safety et al, 2013). The website www.mrisafety.com maintained by Frank G. Shellock is an online updated information resource for MRI safety and bioeffects (http://www.mrisafety.com/).
A particular concern is the safety of MRI in patients with deep brain stimulation (DBS) devices. Tagliati and colleagues performed a survey in 42 centres on MRI use and DBS, and in one case MRI was associated with failure of the pulse generator without neurological sequelae after the replacement of this DBS component (Tagliati et al, 2009).

1.4.2 Gradient magnetic fields

Gradient coils are used to produce deliberate variations in the main SMF. There are usually three sets of gradient coils, one for each direction of space. The gradient magnetic fields are involved in selecting image plane and slice and spatial encoding of detected MRI signal, being important for image quality. They change rapidly during the imaging process both in amplitude and polarity and may induce currents in conductive materials associated with implants (with consequent heating or vibration and eventual damage of devices or heating of the body) and within the body (originating peripheral nerve and muscle stimulation) (Health Protection Agency, 2008). The rapidly changing fields induced by the gradient coils will preferentially stimulate the myelinated nerves, but its thresholds are well below those able to induce ventricular fibrillation (Health Protection Agency, 2008). However, people with epilepsy or taking drugs that lower seizure threshold may exhibit increased sensitivity to stimulation by the electric fields induced in the central nervous system, and these people should be imaged with

caution (Health Protection Agency, 2008). The effects are minimized by avoiding crossing hands or ankles and avoiding wire loops touching the subject.

Time-varying magnetic fields associated with gradients are responsible as well for acoustic noise (vibration of the coils working in the SMF) that is more intense the better the performance of the gradients and the stronger the static field (Health Protection Agency, 2008). Although there is little risk of a permanent threshold shift in hearing in those exposed to MRI-associated noise, certain scans may be uncomfortable, particularly for sensitive individuals (Health Protection Agency, 2008). Patients or volunteers should be adequately protected with earplugs.

1.4.3 Radiofrequency fields

Radiofrequency coils behave as the antennae of the MRI system that broadcasts the RF signal to the subject and/or receives the return signal. The head of the subject is normally placed inside a coil that resembles a birdcage, commonly used for brain imaging. The birdcage coil provides the best RF homogeneity of all the RF coils. Exposure to RF energies may result in heating of the human tissues or eventual implanted devices. Exposure to RF fields of sufficient intensity can induce heating in biological tissue, while effects in the absence of heating remain controversial (Health Protection Agency, 2008). There are restrictions in place for exposure to RF fields during MRI procedures to limit potential body heating. There are uncertainties concerning effects of increased heat loads on infants and pregnant women, and on people with impaired thermoregulatory ability as a result of age, disease or the use of medications (Health Protection Agency, 2008). These people should be imaged with caution.

1.4.4 Other considerations

There are no published studies of mortality or cancer incidence among either patients or volunteers undergoing MRI procedures. However, there have been many epidemiological studies undertaken on people exposed either to power frequency magnetic fields or to RF fields in non-MRI situations. Taken as a whole, the scientific evidence has not clearly demonstrated adverse health effects, although there is evidence of an association between long-term exposure to residential power frequency magnetic fields and a raised risk of childhood leukaemia (National Radiological Protection Board, 2001; International Agency for Research on Cancer, 2002).

Reproductive and developmental outcomes in relation to the use of MRI have been examined in a number of studies. For example, a cross-sectional postal survey conducted in 1990 examined reproductive health among women employed at most of the clinical MRI facilities in the USA (Evans et al, 1993). Based on 287 pregnancies that occurred while working at an MRI unit, as compared with 964 pregnancies that occurred during work in another job, the relative risks for various reproductive outcomes (delayed conception in planned pregnancies, miscarriage, delivery before 39 weeks, low birth weight and sex ratio of babies) were all close to one and none of the differences was statistically significant (Evans et al, 1993).

1.5 Applications of the technique

Functional MRI has achieved a scientific impact comparable to other important biomedical discoveries (Rosen and Savoy, 2012). It is better implemented in neuroscience research, in particular in cognitive neuroscience, than in the clinical practice. It has contributed remarkably, for example, to our understanding of memory, reward circuitry, brain plasticity, resting state networks and social behaviour (Rosen and Savoy, 2012). In the clinical setting, fMRI is mostly used for planning of neurosurgical interventions, although it is not still widely adopted (Bullmore, 2012). Moreover, in spite of its considerable impact in the comprehension of neurological and psychiatric diseases, it does not yet have a relevant role in the diagnosis of these pathologies (Rosen and Savoy, 2012).

The fMRI field has also extended to areas that pose more complicated ethical and philosophical dilemmas, like the research on conscience, moral cognition, decision-making and free-will (Greene et al, 2004; Owen et al, 2006; Soon et al, 2008). And, in recent years, there is a growing interest in complex human faculties for which there are no adequate animal models (Hasson and Honey, 2012), such as music perception (Hannon and Trainor, 2007), neuroaesthetics (Cela-Conde et al, 2011), and the perception of art (Ishizu and Zeki, 2011).

There are many challenges associated with the translation of functional brain imaging research to applications in the broader social arena. For example, Jones and colleagues identified areas where neuroimaging is already having an impact on legal practice: third-party judging, lie detection, determination of mental states, memory, adolescent brain development and culpability of conduct and brain-based appeals

(Jones et al, 2009). Other controversial applications of fMRI technology are neuromarketing (Ariely and Berns, 2010) and politics (Knutson et al, 2006), among others.

1.6 Future of fMRI

The future of fMRI, as seen by Russell Poldrack, will have more methodological rigor (Poldrack, 2012), because many of the limits of fMRI, as previously discussed, are the limits of its own analytic methods. Bennett and colleagues scanned a dead salmon using a social cognition task (!) and found activation when using a threshold not corrected for multiple comparisons (Bennett et al, 2010). Unfortunately, a minority of papers is still published using methods that are improperly corrected for chance, considering the enormous number of tests conducted when analysing an fMRI experiment, and therefore with a high risk of false positives (Bennett et al, 2010).
Among the expected directions in the fMRI field is a greater focus on selective inference, powered by open large fMRI databases and increased use of computational models to describe brain processes. Additionally, instead of concentrating on localization of brain function, increasing focus will be put on understanding connectivity between brain regions, and patterns of activations (Poldrack, 2012).
An ongoing project that likely will produce extraordinary evidence for the understanding of the brain in the coming years is the Human Connectome Project (http://www.humanconnectomeproject.org; van Essen and Ugurbil, 2012). It aims to chart human brain functional and structural connectivity in a large population using cutting-edge neuroimaging techniques, including task fMRI and resting state fMRI. The resultant datasets are being made freely available via an online platform (http://www.humanconnectomeproject.org).

Functional MRI may play a more important role in clinical medicine in the future (Bullmore, 2012). Compared to task fMRI (used today for the planning of neurosurgery of intracranial lesions that are close to cortical eloquent areas), resting state fMRI as a potential clinical tool has several advantages. It does not require patients to perform challenging paradigms, and acquisition takes no more time than a conventional MRI sequence. Brain function can thus be measured in unconscious patients, in patients with dementia or with other important neurological impairment. Also, with a single

scanning session multiple brain networks can be studied at the same time and image interpretation is not influenced by task performance. Moreover, many brain disorders already being investigated with resting state fMRI are expected to have fMRI phenotypes at the level of large-scale brain networks, possibly useful for clinical diagnosis and prognosis (Bullmore, 2012).

Another fMRI application that may be of relevance for clinical medicine for drug discovery and development is pharmacologic MRI (phMRI) (Jenkins, 2012). It possible to elicit neuronal activity using various pharmacological agents as stimuli, including challenges with cholinergics, serotonergics, cannabinoids or opioids. Likewise it is possible to use drugs as a means of modifying the response to other fMRI stimulus, such as cognitive tasks (Dodds et al, 2009).

In the clinical setting it is expected that MRI systems with field strengths higher than 3 T will be adopted because they allow better spatial resolution, which can be important for the study of common diseases like multiple sclerosis (Tallantyre et al, 2010) or epilepsy (Henry et al, 2011). Ultra-high fields are important as well for studies based in magnetic susceptibility contrast, like BOLD imaging, increasing sensitivity, specificity and resolution (capable of working at the level of cortical columns) (Duyn, 2012; Yacoub et al, 2008). Moreover, they allow the use of new contrasts for structural and functional imaging (Duyn, 2012; Yacoub et al, 2008). There are however drawbacks of increasing field strength for fMRI, related to physiological noise (Kruger and Glover, 2001), and economic, technological and biological limitations (higher risk of tissue heating and sensory stimulation) (Duyn, 2012).

Imaging genetics is a research approach in which genetic information and fMRI data in the same subjects are combined to define neural mechanisms associated with genetic variation (Hariri and Weinberger, 2003). This relatively recent research area has had an important role in understanding neuropsychiatric phenotypes (Meyer-Lindenberg, 2012). Initial studies investigated single genetic variants or small deletions, but the field is moving to investigate the full complexity of the genome, making large-scale collaborative work essential (Meyer-Lindenberg, 2012).

1.7 Neuroethics and fMRI

Neuroethics addresses ethical, legal and social implications of neuroscience clinical practice and research findings and with the nature of the research itself (Illes and Bird, 2006). From the discussion above, it is clear that fMRI as a neurotechnology raises numerous ethical challenges, some unique to the field and others not significantly different from other issues encountered in bioethics. Challenges arise from the fMRI technique itself, and concerns that derive from functional imaging research findings, which enhance our understanding of the neural mechanisms of conscience, emotions, personality and social behaviour (Roskies, 2002).

Although a review of the literature from 1989 to 2005 reported a steady increase in the number of articles published on neuroethics, in this period only seven European countries (Belgium, Italy, France, Netherlands, UK, Germany and Spain) published more than five articles (Lombera and Illes, 2009). Moreover, few articles were reported that discussed both fMRI and ethical, legal, or social implications, and even fewer direct citations between the two literatures were identified (Garnett et al, 2011).

In Part Two of this document we pinpoint the ethical issues associated with fMRI in an integrated view, and propose recommendations to address these challenges that may be of use for all stakeholders involved in the field. A list of references is also suggested for a general overview of the problems in question. Furthermore, we hope this document contributes to raising awareness to ethical concerns related to functional neuroimaging in the European context.

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Part Two

Recognizing and Addressing fMRI Ethical Concerns

2.1 Limits, validity and interpretation of fMRI studies

Ethical use of fMRI requires understanding of the limits of the technique and the factors influencing its validity and interpretation. Functional magnetic resonance imaging does not measure neuronal activity directly, but the consequential changes in blood flow and oxygenation. The phenomenon of neurovascular coupling is also well studied, although there is some debate about this in the literature (Attwell and Iadecola, 2002). Other methods of measuring brain activity, such as EEG, are more closely related to the electrical activity of neurons and hence have better temporal resolution than MRI, however they are not true three-dimensional imaging modalities. Compared to PET, fMRI has superior temporal and spatial resolution. An understanding of the measurement of these mechanisms and the underlying assumptions are key in the planning of an fMRI experiment, as well as for the correct interpretation of a result.

Many other factors can influence fMRI validity and image interpretation. These include the manner of stimulating the brain in order to obtain meaningful information (paradigm design), magnetic field strength, MRI acquisition parameters including study length, subject collaboration and head movement (particularly task-correlated motion), presence of non-trivial structural changes in the brain, and image processing methods and statistics (Bell and Racine, 2009; Seixas and Ayres-Basto, 2008; Seixas and Lima, 2011). Moreover, interpretation of data depends not only on scientific frameworks (it is to be noted that a normal reference of brain function, with respect to fMRI, does not yet exist), but also on the cultural and social context (Illes and Racine, 2005). Considering the potential for variability, comparison of fMRI data across research centres is also problematic.

A distinction also needs to be made between fMRI research experiments, which are more focused on group data and in making inferences for the population, and fMRI as used in clinical neuroimaging (for example for planning the surgical removal of a brain lesion) that is focused on results from the individual patient (Desmond and Annabel Chen, 2002). Comparing analysis of fMRI data of a single subject with fMRI group analysis is a good exercise in order to understand some of the problems related to the

validity and interpretation of the technique.

Statistical methods developed for fMRI are usually designed to detect activation rather than characterize it. In single patient clinical studies, the extension of the statistical maps is of importance for the surgeon to better plan an intervention, where in research fMRI, detection is often sufficient. Moreover, in individual subject studies false negatives are critical, to ensure that the absence of activation does not have a deleterious consequence for the patient (e.g. the potential injury of a brain region following surgery, which is not involved in an eloquent function such as language or vision), and so lower statistical thresholds may be desirable. Methods of correction for multiple comparisons have been developed for fMRI group analysis, and are mostly concerned in the reduction of false positives. Stringent alpha-correction levels are also often used to reduce false positives, but this strategy limits statistical power that is key for single subject analysis (Yarkoni, 2009). Increasing sample size (in the case of group studies), scanning time or the number of sessions also increases statistical sensitivity (Loring et al, 2002).

Functional MRI is a complex technique, which requires expertise in several domains. Interpretation of results at times may be speculative, and there is a tendency toward localizing and modularizing brain functions (Hardcastle and Stewart, 2002). On the other hand, the brain may exhibit complex patterns of activation, but not all of the activations may be necessary for performance.

There is sometimes unwarranted anticipation surrounding new or expected uses and there should be caution with respect to premature translation to the market, the legal system or the classroom. Functional MRI imaging is being used non-clinically in the study of cognitive processes such as memory, language acquisition, antisocial behaviour, gender differences behaviour, spiritual experiences, decision-making, lie detection, legal testimony. Indiscriminate and uncontrolled use of this technique can lead to data protection issues and ethical implications for possible discrimination and stigmatization, as well as resulting possible dual use. It can lead to children being streamed pre-emptively into educational programs, with no possibility of bettering their development and low selfesteem (Meyer-Lindenberg A, 2012).

2.1.1 Recommendations

- The adequate method of study of the brain functions to answer specific clinical or research questions (fMRI, PET, EEG or other), should be selected taking into account these techniques relative advantages and limitations, and not just based on accessibility, costs or novelty. Sometimes more than one method may be necessary to better inform on a particular scientific or clinical problem.

- Conclusions about the role of a particular brain region in specific situations should be based on a convergence of information, not just a single fMRI experiment. Integrated views of the brain functioning should be encouraged.

- Validation and development of standardized paradigms/tasks, scanning procedures, and analysis methods for fMRI should be stimulated, whenever possible. The field should look for normative patient and healthy subject data. Organised cooperative efforts across research and clinical centres are recommended, which aim at standardization and creation of large fMRI databases (and of other types of data) (van Essen and Ugurbil, 2012). Such data will be of major importance in the advancement of neurobiological knowledge and imaging methods and in optimising resources. Examples include The Human Connectome Project (http://www.humanconnectomeproject.org/), The Alzheimer's Disease Neuroimaging Initiative (http://www.adni-info.org/) and the UK Biobank (http://www.ukbiobank.ac.uk/).

- It would be useful in the fMRI field to develop a standard code, as for example Current Procedural Terminology (CPT) that is a listing of descriptive terms and identifying codes for reporting medical services and procedures (American Medical Association, 2007). The purpose of CPT is to provide a uniform language that accurately describes medical, surgical, and diagnostic services, and thereby serves as an effective means for reliable nationwide communication among physicians, and other healthcare providers, patients, and third parties (coders, accreditation organizations, medical insurance companies, etc.). This would increase inter-use reliability of fMRI.

- It must be insured that researchers and clinicians, and other relevant stakeholders, involved in the fMRI field have sufficient expertise in the different

competences required, understand fMRI limitations and are able to correctly and clearly communicate results. It is important that particularly the non-specialists are taught about the interpretation, limitations and possible misuse of fMRI results. This should be carried out by means of training of ethical standards within the relevant professions rather than imposition through external regulatory processes (Fenton et al, 2009).

- Patient and healthy volunteers' consent forms should reflect uncertainties related with the technique (Rosen and Gur, 2002).

- Heightened awareness of fMRI challenges and limitations should prevent premature uses of the technique (Racine et al, 2005). These are of concern mostly in the applications of the technique in new areas of research or outside the medical research and clinical environments. At the same time, open-minded and multidisciplinary approaches to new applications of fMRI should be supported, in order not to constrain advancement of knowledge in the field.

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2.2 Safety and ethics

Increasing involvement of fMRI technology and its extension to neuroscientific non-clinical research applications must recognize ethical issues in terms of acceptability of safety issues, particularly in case of high magnetic field equipment of 3 T and above. Partly, ethical acceptability depends on adequate protection of the safety of participants, both patients and healthy volunteers.

There is definitely a need for standardized guidance to assist applicants for ethical approvals in reviewing the issues posed by fMRI research in terms of safety and protection of participants. One of the major goals of this workgroup is the protection of human participants by developing a list of "points to consider" for investigators undertaking fMRI research. Given the rapid evolvement of the technology such a list should be updated regularly.

2.2.1 Recommendations

This section is organized in steps which consider the successive stages of organization of a safety strategy for an MRI environment, including safety measures to control access to the MRI facility, training of personnel and operating procedures, emergency procedures in clinical and non-clinical settings, screening procedures of participants and accompanying persons, MRI exclusion criteria, screening for pregnancy, procedures in place for ensuring safety during scanning.

2.2.1.1 Safety measures to control access to the fMRI facility

- Facilities, clinical and non-clinical, must organize a standard zoning system to regulate access to the fMRI facility safety purposes (zone 4 to zone 1).

- *Zone 4* is housing the MRI scanner and must fall within zone 3. Zone 4 pertains to the risks due the magnetic forces of the SMF of the magnet (with a risk to induce metallic projectiles) and the effects of the time-varying gradient and RF fields when imaging procedures are in progress. At the entry to zone 4 a sign must clearly indicate the presence of the magnetic field and its potential danger.

- *Zone 3* surrounds zone 4, and includes all areas that potentially pose a risk. Typically zone 3 includes the console of the scanner, equipment rooms, and preparatory areas. Rooms within zone 3 may or may not fall within the fringe

fields of the magnet: the “five Gauss line” (1 Tesla = 10,000 Gauss). The boundaries of the 5 G line must be clearly marked: usually with a red line on the floor and with signs reminding the presence of the magnetic field and its risks. This applies particularly to fMRI facilities in non-clinical settings. In addition, appropriate signs must clearly remind that "The magnet is always on" and that persons with pacemakers or prostheses are at risk for accidents. No unscreened non-MR personnel are allowed access to zone 3. Access should be restricted with key locks, pass key locking systems, excluding combination locks. Zone 3 may possibly involve areas of the surrounding building that fall outside of the scanning facility: these additional areas and the risks they present must be marked clearly.

- *Zone 2* is the interface between the freely accessible zone 1 and the strictly controlled zones 3 and 4, which pose a risk. Passage from zone 2 to zone 3 must be impossible for participants not accompanied by qualified MR personnel. Zone 2 may be used for first contact and screening procedures.

- *Zone 1* is freely accessible to the general public, for example waiting rooms. Zone 1 is definitely outside the environment in which the magnetic field constitutes a possible risk.

2.2.1.2 Training procedures for personnel

- MRI facilities present serious potential dangers to untrained or improperly screened personnel, be it clinicians, scientists or radiographers. Also there is a definite need for appropriate training for all individuals who operate the equipment. Certified training procedures, including didactic training in the field, must be organized for each level of authorization. Applicants must clearly document procedures for training and certifying personnel at all levels and keeping certifications current.

- *Level I* personnel are authorized to have unsupervised access to the MRI suite, but may never operate the equipment, including anesthetists, maintenance and transportation staff. They are able to screen themselves and are familiar with safety procedures for entering the MRI suite and are familiar with basic emergency procedures.

- *Level II* personnel are those who, in addition to Level I certification, are also certified to operate the MR equipment, as well as to screen others for entry into zones 3 and 4. Training must include in depth knowledge of MRI safety issues including the safety of different materials. Whenever relevant, training will include elements of RF thermal safety issues and use of contrast agents and their side effects. They must be familiar with safety aspects of claustrophobia and panic state management.

- *Level III* personnel are senior staff members who are fully certified to train and certify Level I and Level II personnel. Such personnel must have knowledge and experience to run a safe MRI environment. The designated safety officer must be a senior level III staff member.

- All researchers should adhere to an accepted national standard of care consistent with safety provisions, similar to those of the American College of Radiology (ACR) (Expert Panel on MR Safety, 2013). Final responsibility for the safety of the MRI examination will at all times rest with the principal investigator or the radiologist (respectively in a research or clinical setting), the safety officer and the MRI facility director.

2.2.1.3 Adequate procedures for dealing with emergencies

- Facilities must at all times be ready to anticipate potential emergencies and to ensure the availability of highly competent personnel coverage. This implies the continuous presence of at least two trained staff members whenever a participant or accompanying person is present in zones 3 or 4.

- A duly licensed physician must be on site to deal with any medical issue, e.g., management of panic states, cardiac problems, acute psychiatric symptoms, etc. Especially for all cases in which an MR contrast is administered (although it is rarely used in the context of an fMRI scan), a physician must be on site to handle possible adverse reactions to the administered contrast.

- Personnel involved in the scan session must be made aware of the designated safety officer: it is important that a single Level II individual is in charge of safety

issues in order to avoid ambiguity or diffusion of responsibility during an emergency prior to entry into the facility.

- Procedures for dealing with emergencies are of utmost importance to maintain staff readiness to deal with emergencies, both in medical settings as in non-medical settings. Knowledge of urgent contact procedures with emergency resources in the facility and community is very important. The staff must be regularly trained in urgent removal and evacuation of a participant from the scanner. The radiographer must be aware when and how to quench urgently the magnetic field.

- If participants have pre-existing medical conditions or are from a vulnerable population, e.g. psychiatric patients, then a qualified member from the research team, who is trained in responding to these conditions, must be in attendance during the MRI scan.

- Note that for scans performed in non-medical settings, it must be made clear to participants in advance that emergency medical services are not readily available onsite.

- The relevant services (such as ambulance and fire departments) should be made aware of the special circumstances that apply when entering a MRI facility. Meetings with such services must be regularly organized in order to familiarize them with safety considerations and for updating their emergency procedures.

- Facility's risk management reporting process includes systematic reporting of all incidents and all adverse events associated with MRI in order to improve safety. All near-accidents revealing breaches of safety procedures and other safety-related incidents should be reported, as they might reveal weaknesses in safety procedures.

2.2.1.4 MRI safety screening procedures for personnel and of participants

- It is important to underline the necessity of routine careful screening of all individuals who enter the MRI facility, i.e., all radiographers, all accompanying caretakers and participants who enter the MRI facility.

- It is good practice to use standard screening forms for example the MR Safe Practice Guidelines to be obtained from the ACR (Expert Panel on MR Safety et al, 2013) or to be downloaded from www.mrisafety.com or www.IMRSER.org. A qualified interviewer must review the screening form with the participant item by item to make sure that the participant has fully understood each item and that there are no contraindications to scanning. It is advocated to include a second approach to screening to provide redundancy and increase safety. Thereby is must be double-checked that participant is free of surface metallic objects that may be unsafe for MRI: jewellery, coins or other metals.

- In fMRI experiments that involve a task to be performed by the subject during the scanning session (for example a motor task), before entering the equipment participants should be trained in performing the necessary task, when possible. A mock scanner may be useful to familiarize them with performing complex fMRI tasks in this particular environment.

- The participants' ability to comply with the MRI procedures should be evaluated in terms of sufficient comprehension, eventual mental impairments, and ability to remain focused. When there are concerns about the participant's comprehension, it may be needed to obtain the necessary safety information from the legal caretaker. In these cases it may also be desirable that the caretaker accompanies the participant during the scanning session. Informed consent procedures of vulnerable subjects for fMRI experiments will be covered in sections 2.4 and 2.6.

- Also, the final responsibility for ensuring that it is safe for the participant and/or accompanying persons to enter the MRI environment rests with the research facility an the scientific investigator who have the authority to deny or authorize entry into the MRI facility.

Notes: Availability of a high strength magnet (1000 G or more) as a supplement to screening may be useful but should not replace the screening interview, given the risk of false negatives. Ferromagnetic detectors such as hand-held, wall-mounted and walk-through models constitute a potentially useful supplement. However, such devices should be systematically validated and, at this stage, should not replace thorough interviewing procedures.

2.2.1.5 MRI exclusion criteria

- Cardiac pacemakers, aneurysm clips, cochlear / retinal implants, hearing aids, permanent eye lining, tattoos, metal plates / pins / screws on bones / deep brain and other stimulation devices: these devices or materials may sometimes preclude an MRI exam. Checking procedures for verifying the safety of implanted devices are mandatory and include contact with the manufacturer, published information, web-searches and educated opinions of qualified safety experts. MR safety information may be less readily available for field strengths higher than 3 T.

- Patients or volunteers that were exposed to metallic flakes and/or that had a metallic injury cannot have a MRI scan unless they have an X-ray showing absence of embedded metal in the body. Permission for screening with ionizing radiation (X-rays) needs to be obtained in advance.

- Persons suffering from real claustrophobia or those who feel uncomfortable in small, enclosed spaces, like the MRI tunnel, should not be scanned for scientific reasons. For clinical purposes sedation may be indicated, although it can alter fMRI results. The use of sedatives for an MRI study only for scientific reasons is not ethically acceptable. Similarly, it is also not ethically acceptable to sedate patients/healthy volunteers to prevent small movements during the scanning session. For subjects who feel uncomfortable in enclosed spaces it may be of help for them to visualize the scanner room and/or to watch a film about the normal MRI procedures before the study.

2.2.1.6 Screening for pregnancy in women of child-bearing age

- Ethical acceptability – or not – of exposing pregnant mothers and fetuses to MRI scanning without compelling clinical indications, will be discussed in a separate chapter. In any case, there is an absolute need to put in place an appropriate screening program to exclude pregnant participants. Thereby the usual ethical issues are raised in terms of confidentiality.

- Some recruitment procedures merely ask during the consent/assent process if there is a possibility she may be pregnant and note the date of the last menstrual period and/or whether there has been unprotected sexual activity. Other centres test routinely for pregnancy in all females of child-bearing age. However, routine pregnancy testing raises a number of ethical issues as the testing holds implications for the disclosure of such results. For example,
    - Having the parents first learn of an adolescent's sexual activity;
    - Cultural influences – the screening process may be harmful for the adolescent female and/or her family;
    - Accidental disclosures of pregnancy to accompanying persons.

- Applicants must fully document the strategy on how to deal with pregnancy as incidental finding. In any case, screening involving pregnancy testing must be in compliance with the local applicable law. To avoid these ethical issues, pregnancy might be mentioned as a reason not to volunteer at the time of recruitment.

2.2.1.7 Standard procedures in place for ensuring safety during scanning

- It is important that the participant is visible to and in hearing contact with the MRI operator at all times. The possibility to voluntarily terminate a study at any time during scanning must be foreseen in accordance with the Declaration of Helsinki (World Medical Association, 2013).

- Earplugs or other hearing protection should be used during scanning to attenuate noise levels. Acoustic noise levels during scanning indeed reach more than 120 dB, depending on pulse sequence, field strength, etc. Risks will vary given single versus repeated exposures and scan duration. Hearing protection typically lowers these exposures by about 20 dB, depending on the type of

protection. Even with optimal hearing protection, a weighted root mean square sound pressure level greater than 99 dB poses a significant risk. For participants that already suffered a noise-induced hearing loss, caution must be taken to avoid further damage. The following FDA document is relevant for guidance on this subject: "Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices", dated July 14, 2003 (U.S. Food and Drug Administration, 2013).

- For adults, children, and infants greater than one month of age, field strengths greater than 8T are presently considered to pose a potential significant risk. Specific neurocognitive domains were proven to be affected by movement-induced time-varying magnetic fields within a SMF of a 7T MRI scanner. Domains that were affected included attention/concentration and visuospatial orientation. Especially attention and concentration were negatively affected when exposed to time-varying magnetic fields within a SMF varying from 5.0% to 21.1% *per* Tesla exposure ($p<0.05$), particular in situations were high working memory performance was required. In addition, visuospatial orientation was affected after exposure (46.7% *per* Tesla exposure, $p=0.05$). These side effects are distressing and may challenge the ethical acceptability to use these fields of 7T and higher in patients/volunteers. More studies are needed to investigate secondary effects of ultra-high magnetic fields and their duration, particularly cognitive effects that are more difficult to measure and less likely to be spontaneously reported by the patients or healthy volunteers.

- The *specific absorption rate* (SAR) is the RF power absorbed *per* unit of mass of an object and is expressed in watts *per* kilogram. The SAR describes the potential for heating of the subject's tissues due to the application of the RF energy necessary to produce the MRI signal. The SAR increases with field strength. The SAR limits vary from country to country, but in most countries standard MRI systems are limited to a maximum SAR of 4 W/kg. The following limits were proposed by the FDA (U.S. Food and Drug Administration, 2013):
    - Whole body average dose over 15 or more minutes: 4 W/kg;
    - Head average dose over 10 or more minutes: 3 W/kg;
    - Head or torso dose per gram of tissue over 5 or more minutes: 8 W/kg;
    - Extremities dose per gram of tissue over 15 or more minutes: 12 W/kg.

- Any rate of change of gradient fields (dB/dt) sufficient to produce severe discomfort or painful nerve stimulation is considered a significant risk.

2.2.1.8 Other risks and discomfort associated with fMRI experiments

- As seen above, the risks and safety issues of an fMRI scan are identical to those of a conventional structural MRI exam. But an fMRI experiment may include a stimulus that can pose eventual risks or discomfort to the subject, beyond the actual scanning procedure. Examples are fMRI experiments investigating visceral pain, in which an inflating balloon may be inserted in the oesophagus or the rectum of the patient or healthy volunteer to elicit pain or other visceral sensations (Bonaz et al, 2002; Hojo et al, 2012).

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2.3 fMRI in pregnancy: safety issues and ethical considerations

Magnetic resonance imaging is generally considered safe during pregnancy, as magnetic energy has been shown not to be harmful for the developing fetus (Shellock and Crues, 2004). However, there is still a paucity of published data from studies evaluating the long-term safety of MRI examinations in pregnancy (de Wilde et al, 2005). A small number of animal studies pointed to possible teratogenic effects of MRI exposure in early pregnancy. A reduction in crown-rump length was seen in mice exposed to MRI in mid-gestation (Heinrichs et al, 1986). Exposure to the electromagnetic fields simulating a clinical study caused eye malformations in a genetically predisposed mouse strain (Tyndall and Sulik, 1991). Several hours of exposure of chick embryos within the first 48 hours of life to a strong SMF and rapid electromagnetic gradient fluctuations resulted in an excess number of dead or abnormal chick embryos, when examined at day 5 (Yip et al, 1994).

Although not directly applicable to humans, these findings provide some cause for concern regarding fetal MRI in the first trimester. From there, it is generally recommended as a measure of prevention to screen females of reproductive age for pregnancy before permitting them access to MRI environments. Also, the guidelines of the UK National Radiological Protection Board stated that "it might be prudent to exclude pregnant women (patients and volunteers) during the first three months of pregnancy" (National Radiological Protection Board, 1991).

Though permitted to work in and around the magnetic resonance environment, pregnant health care practitioners are requested not to remain within the scanner bore or zone 4 during actual data acquisition or scanning.
In addition, one must also consider that in case of MRI scanning in early pregnancy, patients may blame the procedure if later a fetal malformation is detected. The relatively high rate of spontaneous abortion in the first trimester is also a reason for concern. An MRI study could be coincidentally followed by a spontaneous abortion, but might give rise to parental culpability feelings regarding causal effect.

Precautions should be taken to avoid scanning in pregnancy and practitioners should reassess the potential risks versus benefits of the scanning. It is highly recommended to postpone the MRI examination to the end of the pregnancy, if possible. Pregnant

patients should only undergo MRI scans, at any stage of pregnancy, when it is not prudent to wait until the patient is no longer pregnant.

Paramagnetic MRI contrast agents should not be injected into pregnant patients. Indeed, part of the gadolinium-based MRI contrast agents readily enters the fetal circulation. They will be excreted by the fetal kidneys into the amniotic fluid. Gadolinium-chelated molecules will remain in the amniotic fluid for an indeterminate amount of time. The fact that chelated molecules remain in the amniotic fluid is worrying as the dissociation of the potentially toxic gadolinium ion from its ligand increases with time. It is unclear what impact such free gadolinium ions might have on the fetus. It must thereby be reminded that animal studies have already demonstrated increased rates of spontaneous abortion, skeletal abnormalities, and visceral abnormalities when given at 2–7 times the recommended human dose (U.S. Pharmacopeia, 2004).

Moreover, the decision to administer a gadolinium-based contrast agent to pregnant patients can only be decided after a very thoughtful risk/benefit analysis. Paramagnetic agents are not recommended in pregnancy by FDA because they cross the placenta and their long-term effects are unknown (Kanal et al, 2007). European Society of Radiology guidelines state that gadolinium-based contrast agents are probably safe in pregnancy, but they should only be considered when absolutely necessary (Webb et al, 2005).

2.3.1 Recommendations

- From the safety data and ethical considerations outlined above, one must exclude pregnant women (patients and volunteers) during the first three months of pregnancy from participation in projects using fMRI.

- An ethically acceptable screening process must be put in place to detect pregnancy in participant women of child-bearing age.

- Given the possibility of spontaneous abortions or fetal malformations, applicants should exclude participants that are likely to develop culpability feelings regarding a possible causal effect.

- Administration of gadolinium-based contrast products merely for scientific reasons is considered to be non-ethical given the principle of precaution.

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2.4 fMRI in children and the fetus: ethical acceptability?

Since little is known about the effects of SMFs on growth and behavioural development of fetuses and infants, and hence a minimal-risk standard is difficult to define, caution is suggested concerning the use of fMRI in these scenarios (Fenton et al, 2009; Health Protection Agency, 2008; Hinton, 2002). The physical and psychological risks of the MRI procedure, explained in the previous section, may not exceed minimal risk in pediatric imaging (Davidson et al, 2003; Matthias et al, 2011; Rosen and Gur, 2002; Rosenberg et al, 1997). However, the sedation and contrast enhancement that are sometimes associated with MRI research (but rarely in the more specific context of fMRI) seem to exceed the level of risk encountered by typical, healthy children in their everyday experiences.

Five specific scenarios can be considered:

- Children in good health, too young to give their assent;
- Healthy school-aged children and adolescents able to give their assent that are invited to participate in scientific studies on cognitive brain physiology;
- Sick children that need anyhow MRI or fMRI scans for diagnostic or follow-up reasons in which additional scanning is planned for clinical scientific reasons;
- Children who suffer from mental, psychiatric or neurological conditions, who do not need to undergo fMRI for diagnostic reasons, but are asked to participate for clinical science reasons. These patients might eventually benefit from the studies: early or improved diagnosis, guided neurosurgery or drug treatment;
- The fetus, usually imaged with MRI to rule out or to confirm suspicious findings on fetal ultrasound.

Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research (World Medical Association, 2013). Injection of a contrast agent for MRI examination carries a small but real risk of allergic reaction, and the risk of local and minor systemic reactions from MRI contrast agents varies from 4 percent to 6 percent. Therefore, it is our opinion that MRI with contrast enhancement does not meet the minimal-risk standard for research with healthy children or healthy adolescents.

With respect to the possibility of psychological harm, in studies of children aged 10 to 18 years old who had MRI scans, 12 percent said they felt disturbed by the confined space, 16 percent said they were bothered by the noise, and 1.2 percent could not complete their MRI scan due to claustrophobia. A number of articles have reported that children experience greater anxiety or fear during MRI scanning than do adults. Other authors claimed that there were no significant differences between children and adults in measures of physical comfort, emotional comfort or perception of performance (Thomason, 2009).

One of the greatest challenges to participating in fMRI research is for patients to remain still for the duration of the scan. This is an impossible demand for young children and keeping older children for a prolonged period in this situation is ethically unacceptable due to the excessive physical discomfort they will experience. Sedation to overcome the psychological and physical stress merely for scientific research is unacceptable.
Preventive sedation in MRI protocols can result in added risk for side effects such as gastrointestinal complaints (18 percent to 37 percent) and motor imbalance and transient ataxia (66 percent to 85 percent). In addition, sedation administered purely for scientific reasons does not meet the minimal-risk standard and is ethically very questionable. In children that must anyhow have sedation for clinically justified investigations, the extension of fMRI techniques may be acceptable.
Use of injectable sedatives for panic states or claustrophobia attacks usually causes more severe side effects, and scanning of sensitive children must be avoided at all costs.

All this must be kept into perspective since some studies e.g. that by Schopf and colleagues, have advocated that combined structural and functional data for all gestational ages would allow more specific insight into the developmental processes of the fetal brain (Schopf et al, 2012). While this scientific objective is sound, it is important to consider whether it is ethically acceptable to prolong MRI fetal exams in order to pursue such results.

2.4.1 Recommendations

- It seems ethically unacceptable to perform fMRI in young healthy children that are unable to give their assent as the whole procedure carries a significant risk of inducing anxiety and unacceptable physical discomfort.

- It seems ethically acceptable to recruit children older than 12 years who are able to give their written assent after being fully informed. Indeed, children that do not have the legal capacity to consent to participate in research, may be recruited if they are able to assent, i.e. being capable of having a study explained to them and capable of reading a simple form about it, and giving verbal or written agreement. Parents or legal guardians' permission remains mandatory.

- Investigators must describe how they plan to minimize implicit pressure on such children to participate. As with all consent and assent forms, the freedom to decline participation, without penalty, should be made clear. Children may never be rushed to take their decision during a first meeting. Parents and children must take time to discuss at home whether or not they would like to participate in the study.

- The ethical acceptability for financial incentives that might benefit parents remains highly questionable.

- Most young healthy research volunteers are unlikely to have had previous experience of being scanned. When assent/consent is being sought for participation in research studies, all should be given detailed information about what the scanning process involves and its potential risks. Showing teaching videos and using mock scanners might be helpful in this respect. The mock scanner typically includes recorded MRI sounds, a screen for stimulus presentation/movie viewing, supine positioning of the child on a moving table and button box for the child to key in responses.

- Administration of contrast agent to an MRI increases the odds of harm and makes them unacceptably high when scans are performed solely for scientific reasons.

- Administration of sedatives, especially injections, seems unacceptable when the scans are performed solely for scientific reasons. The risks and benefits should be fully considered in such scenarios.

- Additional MRI and fMRI scans, performed in sick children who need to undergo these procedures for clinical reasons, seem ethically acceptable as the patient's might directly or indirectly benefit from these investigations. In these circumstances contrast administration and sedation seem ethically acceptable.

- Sick children who are or can be involved in the information process must receive verbal explanations of what will happen to him/her and the opportunity for discussion should always be provided. It is always preferable to seek the child's written assent, even when it is not legally required. Parents or caretakers' permission is mandatory.

When planning a research study that will involve children, the applicants must consider four main issues:

- Document rationale for including children. Address the unique outcomes and benefits of studying children. Indicate if the study addresses a medical condition that particularly affects children: e.g. a condition uniquely affecting/manifesting in children. Indicate if the research concerns an area of neuropsychology specifically related to children: e.g. adolescent depression; stages of brain development.
- Document fully the risk level. Indicate the relevant regulations.
- Justify the ethical acceptability to deviate from standard of care for the subjects.
- Fully document the consent procedure, i.e. permission and assent requirements for the study. Indicate the strategies to obtain assent from the child and permissions from parents or caretakers.

- The local institution's Research Boards and/or Ethic's Committees will determine if adequate provisions are made for obtaining the assent of children and evaluate whether the children are capable of providing assent. In determining which children are capable of assenting, they should take into account the ages, maturity, and psychological state of the children. This

judgment may be made for all children as a group under a particular protocol, or for each child individually as the committee deems appropriate.

- At the moment, this working party cannot recommend fetal fMRI, in particular as a routine procedure, because there is no sufficient specific fMRI technical expertise for the fetus, and because in fetal medicine there is a lot of uncertainty on the meaning and prognosis even of structural abnormal findings.

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2.5 Incidental findings

An incidental finding (IF) is defined, according to Wolf and colleagues, as having "…potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study" (Wolf et al, 2008). In fMRI studies, these can be abnormalities found in the structural scans obtained for registration purposes, or unexpected neural activations.

Incidental findings are common with the use of brain MRI and are more problematic in the research setting, where they fall out of the scope of the investigation and many times are discovered outside of a clinical environment by a non-physician. This is even more so if there is the possibility of false positive findings, which may result in unnecessary worries, medical investigations and costs.

In a retrospective study of brain MRI scans of 1000 volunteers who participated as control subjects for various research protocols 18% demonstrated incidental abnormal findings, of which 15.1% required no referral, 1.8% required routine referral and 1.1%, required urgent referral (Katzman et al, 1999). A recent meta-analysis described a prevalence of 0.7% neoplastic brain IFs, and this prevalence seems to increase with age (Morris et al, 2009).

The issue of IFs is being recognized increasingly and many research centres have already in place strategies to deal with them, but no consensus exists regarding the ideal strategy. For example, neuroradiology reviews of research scans are perceived as time-consuming and expensive and potentially exposing institutions to risk (Shoemaker et al, 2011). In addition, there are concerns that receiving a radiology report may cause unnecessary anxiety among research participants, unfairly burden those who are uninsured or cause insurance problems (Shoemaker et al, 2011). Conversely, neuroimaging IFs may have medical importance, and a large majority of research participants seem to prefer to be informed of their radiology review (Shoemaker et al, 2011). However, it is unclear whether these study participants have been duly informed on the potential detrimental social consequences such information can have due to the pre-contractual disclosure duty when applying for example to private life insurance, professional disability insurance etc.

2.5.1 Recommendations

It is important that participants know that an fMRI study is usually not suitable for diagnosis, and whether the research team includes a radiologist trained in reading brain images. They should also be informed that an abnormality may be detected, the clinical significance of which may not be readily clear. The participants must be informed about the path that will be taken in the event that such IF is discovered provided the study participant has given written informed consent to receiving such information and has not decided to make use of his right not to know. The protocol must identify a qualified physician to report such findings to a participant who has consented to receiving such information, and offer support and guidance.

Guidelines on how to handle IFs are needed, and the following recommendations represent the authors' suggestions. Concerning IFs, two research contexts must be distinguished: the therapeutic research context and the non-therapeutic and non-medical research context. It is also of relevance to address the different possible study populations separately: patients, healthy volunteers and vulnerable patients/volunteers (i.e. study participants who are not able to give informed consent).

2.5.1.1 Therapeutic research context

Before fMRI scans are performed in a therapeutic research context where new drugs and/or medical devices/procedures are tested:

- The patient should be duly informed that through the fMRI IFs could occur indicating diseases which could either be handled within the current treatment regime or would make necessary a new or additional treatment regime(s). Since the patient is under treatment and has through this decision shown his willingness to improve/restore his/her health it can be presumed that the patient would like to know about these findings especially in cases where immediate action is needed. Nevertheless in order to respect the patient's autonomy, he/she should be asked whether he/she wants to receive such information.

- There also can be IFs, which indicate diseases for which no treatment yet exists. The patient should be given the opportunity to decide whether he/she wants to be informed about such findings. If the patient wants such information to be given, a specific counselling policy must be developed to help the patient bear the implications of such findings.

- Healthy volunteers should be duly informed that through the fMRI IFs could occur indicating diseases for which efficient treatments already exist. The healthy volunteers should be asked before participation whether they want to be informed about such findings. There could be reasons on the side of the study participant not to be informed about such findings.

- The healthy volunteers should also be asked whether they want to be informed about incidental IFs related to diseases for which no treatment yet exists. If the study participant wants such information to be given, a specific counselling policy must be developed to help the study participant bear the implications of such findings.

- Persons not able to give informed consent should only be included if there is either a clear potential benefit for them personally or the group of patients affected by the same disease, and if the burden imposed on them is minimal, and if they cannot be replaced for study reasons by persons able to give informed consent.

- With respect to this vulnerable population, informed consent has to be provided by the legal representatives. The legal representatives should be duly informed about the procedures to be performed and the possibility of IFs, which indicate diseases for which efficient treatments already exist. They should also be informed that IFs could occur which indicate diseases for which no treatment yet exists. In case such information is provided to the legal representatives, a specific counselling policy must be developed to help the legal representatives and the patient to tackle the implications of such findings.

2.5.1.2 Non-therapeutic and non-medical research context

Before fMRI scans are performed in a non-therapeutic/non-medical research context:

- Patients should be duly informed that through the fMRI IFs could occur indicating diseases for which efficient treatments already exist.

- In order to respect patients' autonomy, they should be asked before participation whether they want to be informed about such findings. There could be reasons on the side of the study participant not to be informed about such findings, though this may rarely occur.

- The patients should also be asked whether he/she wants to be informed about IFs related to diseases for which no treatment yet exists. If the study participant wants such information to be given, a specific counselling policy must be developed to help the study participant bear the implications of such findings.

- Healthy volunteers should be duly informed that through the fMRI IFs could occur indicating diseases for which efficient treatments already exist.

- The healthy volunteers should be asked before participation whether they want to be informed about such findings. There could be reasons on the side of the study participant not to be informed about such findings, though this may rarely occur.

- The healthy volunteer should also be asked whether he/she wants to be informed about IFs related to diseases for which no treatment yet exists. If the study participant wants such information to be given, a specific counselling policy must be developed to help the study participant bear the implications of such findings.

- Persons not able to give informed consent should only be included if the burden imposed on them is minimal, and if they cannot be replaced for study reasons by persons able to give informed consent. Furthermore, this group should stand to benefit from the knowledge, practices or interventions that result from the research. With respect to this vulnerable population, informed consent has to be provided by the legal representatives.

- The legal representatives should be duly informed about the procedures to be performed and the possibility of IFs, which indicate diseases for which efficient treatments already exist. They should also be informed that IFs could occur which indicate diseases for which no treatment yet exists. In case such information is provided to the legal representatives, a specific counselling policy must be developed to help the legal representatives and the patient to tackle the implications of such findings.

- For all volunteers who, prior to participation, choose not to be informed of IFs, researchers should refrain from interpreting scans beyond the scope of the research protocol. It also follows that for these volunteers, absent consent, researchers should not document and/or store any information that exceeds the research scope. This is consistent with data protection laws, and will help minimize potential harms to these volunteers.

2.5.1.3 Insurance

- Study participants undergoing fMRI should be duly informed that IFs, may they be such for which efficient treatments already exist, or such for which no treatment yet exists, have to be disclosed to private insurance companies if requested, for example in case the study participant plans to obtain, or is in the process of applying for, private health insurance, private life insurance or professional disability insurance (pre-contractual disclosure duty).

2.5.1.4. Collaborative databases

- At this moment, recommendations for unexpected neural activations (functional IFs) are difficult to produce because there are no normative data; effort for collaborative databases is encouraged. This is to increase our knowledge on such IFs in health and disease, how to identify them and their meaning.

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2.6 fMRI in the context of neurodegenerative and psychiatric diseases

Functional magnetic resonance imaging has a huge potential in the study of conditions which cannot be understood through brain structural abnormalities alone, including psychiatric diseases, neurodegenerative diseases and unconscious states, for example pre-symptomatic diagnosis of diseases such as schizophrenia, addictive behaviours, dementia, understanding of autism and to distinguish between patients in a minimally conscious state from patients in a persistent vegetative state. It might also be useful in monitoring treatment as in children with attention deficit hyperactivity disorder or dyslexia. This has huge implications for the inclusion of vulnerable persons in such research, from the consent process to long-term consequences from the results of these investigations (Fenton et al, 2009).

Competence and voluntariness of persons undergoing fMRI are key considerations especially for children, elderly and persons with disabilities who have impaired or not yet developed full mental capacity to make full-informed decisions. These persons may be unable to comprehend the full implications of the results from such investigations (Fenton et al, 2009). In these patients, competence cannot be presumed, complicating

recruitment and consent procedures (Anderson et al, 2012). These are issues of consent and capacity and patient's personal and environmental conditions (psychological status, education, expectations, and social support) should drive the physician to partial or full diagnostic disclosure, or delay communication. Furthermore, the results from fMRI investigations may lead to discrimination in provision of health insurance, life insurance, future employment, and education, which can result in discrimination and stigmatization and health care disparities (Meyer-Lindenberg, 2012).

Neuroimaging approaches may also identify factors important in psychopathology such as structural abnormalities, dysfunctional metabolism or activation patterns. This may have implications for the detention of individuals who have not yet committed a crime, but are deemed a potential threat to public safety and some countries, such as UK, is monitoring the data collected in such cases in order to address possible gaps in legislations (Health & Social Care Information Centre, 2013). Such individuals could, for example, be diagnosed with ''Dangerous Severe Personality Disorder'' or DSPD, a term without defined or sanctioned legal or medical status, creating an ethical conflict about the public's right to safety versus the individual's right to freedom (Canli and Amin, 2002).

The claustrophobic nature of the fMRI apparatus may lead vulnerable and impaired persons to experience unnecessary fear, stress and anxiety, leading to the use of physical or drug induced sedation procedures to reduce movement. With careful screening and safety procedures, the long term effects of exposure to the magnetic field are believed to be negligible; however, emotional and physical responses to the stress of prolonged immobility and confined environment must be considered when testing cognitively and emotionally disabled individuals. Presently, performing competent brain imaging requires intensive time commitment and institutional support (Rosen and Gur, 2002).

The field of fMRI is evolving into data-intensive, big data endeavor with large databases and masses of data being shared around the world. At the same time, ultra-high field MRI scanners are now available producing data at previously unobtainable quality and quantity. Both aspects are leading to changes in fMRI data analysis methodology (Lohmann et al, 2013). Moreover, imaging genetics, a research approach in which genetic information and fMRI data are combined to investigate neuromechanisms linked

to genetic variation (Hariri and Weinberger, 2003), is trying to incorporate new sources of biological information such as whole genome sequencing, proteomic, lipidomic and expression profiles, ultimately hoping to improve and create therapeutic options for psychiatric and neurological disorders (Meyer-Lindenberg, 2012). Challenges of big data include data storage, search, analysis, sharing and transfer. Shared databases among neuroimaging consortia can lead to data banks that require specific security and de-identification measures, due to the level of complexity, quantity and quality of the data obtained of individuals and populations and since some cranial features acquired during imaging could possibly be used to re-identify volunteers as well as for example particular genetic profiles. Risks related to the crossing of information and the limits of de-identification and anonymization are considerable, even if the most effective methods are used. Further complicating the issue of brain databases is the discovery of incidental findings on secondary analysis of the data. Lessons learnt from ethical considerations of genetic studies can be used (Illes et al, 2007).

A model example of the ethical implications of fMRI in the context of neurodegenerative and psychiatric diseases is Alzheimer's disease (AD). This has been the subject of extensive reviews and reports, for example from the Alzheimer's Association (www.alz.org) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://www.loni.ucla.edu/ADNI). Functional MRI has been used to increase the sensitivity and specificity in diagnosing AD, predicting who is likely to develop AD, and development alternative surrogate markers. Ethical issues have been organised thus: the medical and social consequences of predicting AD using functional neuroimaging, e.g. new meaning of the disease, and differentiating different clinical subtypes of AD; scanning protocols and modalities; research and clinical ethics issues, and stigma; key issues for education, counselling, and communication.

The screening of patients will vary depending on whether fMRI is effective at diagnosing the progression of AD or can result in the selection of a possible treatment, which can actually reverse the pathologic changes and cure patients. National and international laws and guidelines for research need to be carefully considered in the research design, especially since there may be a negative risk-benefit for individual AD volunteers often recruited from the pool of vulnerable subjects (e.g., mentally disabled persons). Autonomy, cognitive privacy, and cultural sensitivity should also be considered as highlighted in the Belmont Report (Illes et al, 2007).

2.6.1 Recommendations

Results from fMRI imaging can lead to tension between academic and medical investigators on the one hand, and commercial service providers and their customers on the other:

- Members of the neuroimaging community should be engaged with ethical issues when they undertake fMRI research, particularly in the context of neurodegenerative and psychiatric diseases. Across various cultures, values differ in terms of what defines benefit and risk, who will benefit and who is at risk, what methods must be in place to assure the maximum safety, comfort, and protection of subjects and patients, and educational and policy needs. Researchers should be motivated by ensuring public understanding, external forces, requirements, values, and press and public.

- Potential barriers should also be acknowledged: lack of resources, administrative burden, relevance to the research, and lack of interest.

- It is always important to consider fMRI in context, i.e. fMRI markers must be correlated to other biomarkers of underlying cellular and molecular mechanisms. It is important to consider translational fMRI in the connectivity paradigm, and clinical decision support, especially in drug response prediction (Bullmore, 2012).

- Persons with neurodegenerative and psychiatric diseases should also be engaged in discussing the potential role of fMRI in mitigating stigma. This can be done by supporting explanations of mental illness as an imbalance of brain chemistry; legitimising psychiatric symptoms, which may have previously been de-legitimised since they lacked objective representation (Buchman et al, 2013).

- It is also important to consider two norms: ethical transparency and ethical reproducibility, i.e. transparent reporting concerning the ethics methods, i.e., design elements related to ethics concerns undertaken in a study and critical engagement with, and learning from, the ethics practices of other investigators (Eijkholt et al, 2012).

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2.7 Implications of fMRI research

Philosophically, fMRI is a biomedical model of health that focuses primarily on biological processes. It is based on a positivistic and individualistic worldview, for example the risk of disease for an individual can be measured and predicted through an objective scientific method (positivism) and the individual has an explicit right to make use of, and personally benefit from, his or her genetic material (individualism). This is consistent with ideas of neuroessentialism: the brain is considered the ''self-defining essence of a person''. Neurogenetics and fMRI is constructed, ultimately, as the key for the blueprint (genetics) to understanding the self (Brief and Illes, 2010).
Yet positivism and individualism are predominant mostly within the context of Western ideas of consent, ownership, confidentiality, and benefit. In research with indigenous peoples or other groups with non-Western cultural practices or moral philosophies, it is thus important to link neurogenetic research with community-based participatory approaches, which consider holistic, rather than reductionist, views on health and wellness.

Reciprocally, fMRI studies have the potential to contribute to philosophical problems. Research using fMRI has been conducted investigating moral reasoning (Chiong et al, 2013), social emotions (Immordino-Yang et al, 2009) and conscience (Monti et al, 2010). Studies investigating conscience with fMRI methods are focus of much debate. A recent fMRI study reported awareness in four out of 23 patients (one in six) by wilfully modulating their brain activity through mental imagery, for example by imagining playing a tennis game, who had been diagnosed as being in a vegetative state (Monti et al, 2010). Functional MRI cannot provide any direct measure about conscious awareness, but can be used to provide diagnostic information about the severity of the patient's functional impairment, based on topological changes of functional brain networks, and this may allow a more accurate prediction of the clinical outcome in the future. Thus there must be careful consideration of technical and methodological limitations with respect to potential patient benefit and burden (Schwarzbauer and Schafer, 2011).

A pragmatic approach to neuroethics in fMRI should also address the challenges and ethical implications from the perspective of patients. Self-identity may be affected by fMRI results, for example in autism. Patient accounts of the experience of living with autism have revealed a view of autism that stands in stark opposition to the biomedical model, since they have unique ways of experiencing the world. To illustrate, Temple Grandin once stated, "If I could snap my fingers and be nonautistic, I would not – because then I wouldn't be me. Autism is part of who I am." The importance of such personal accounts allows us to measure whether researcher and/or clinician priorities are in line with the priorities and preferences of the individuals themselves.

To best serve these particular populations of individuals and their families questions need to be asked, such as what aspects of a person's identity, integrity, and sense of personhood would the results from such imaging techniques bring about? What, if any, level of change is ethically appropriate (Racine et al, 2011)? Functional MRI is posing some serious challenges to our conceptions of free will and moral responsibility.

2.7.1 Recommendations

- The inclusion of different patient cultural perspectives in the conduct of research will help ground research within a concerted and collaborative framework to respect values and social diversity (Racine et al, 2011).

- The understanding of complex, fundamental problems like consciousness benefits from multidisciplinary approaches.

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2.8 Science communication and the power of images

In order to fully appreciate the nature of at least some of the ethical issues that arise from the use of fMRI, a discussion of the power of images and pictures and what they convey will be helpful. Particularly where fMRI is used outside the clinical or neuroscience research setting, i.e., beyond the reach and interpretative expertise of neuroimagers, the reactions these images may elicit within the lay public need to be understood by those using the technique. Brain images, in particular, are arguably more potent than images involving other body organs given the brain's centrality in Western culture and the irresistible inclination humans have to seek simple explanations to even the most complex questions. The media often exacerbate this tendency by oversimplifying the explanatory value of images in neuroscience. (Indeed, neuroscientists may also do this, although likely inadvertently). Even neuroscience itself can confer an aura of credibility when invoked by the press (Kulynych, 2002).

Much has been written about the power of images to persuade. Indeed, there are some images that are so iconic that we can picture them mentally by a mere description of the image. For instance, there are likely few Westerners who would not immediately conjure the correct image at the mention of Leonardo da Vinci's "Mona Lisa." An even more powerful category of images, photographs, have a sort of evidentiary persuasiveness that other types of images lack (Meskin and Cohen, 2008). And it is our reaction to and interaction with photographs that is most at play in fMRI, because brain images have been the preferred media to communicate fMRI science. The lay public, scientists, science communicators in general and the media all play roles in how fMRI

images are perceived and discussed. However this first needs to be understood with respect to the significance of photographs in general.

"Seeing is believing"

From the earliest days of photography, we have been accustomed to understanding photographic images as two-dimensional visual representations of the objects they depict[1]. While not completely literal (due the lack of a third dimension), photos can reveal fundamental information about the characteristics of the subject of the photo. Further, with the exception of photorealist art (e.g., some of the early works of artist Chuck Close), we do not confuse photographs with paintings – we recognize, and give more credence to, photographs. Indeed, in the era of cell phone cameras, Instagram, Pintrest, Facebook, Twitter, etc., we have become ever more receptive to documenting and sharing visual representations of ourselves and/or the things around us. We value photographs as the next best thing to "being there." There is a marked difference in how we react to hearing about devastating natural events (earthquakes, tsunamis, hurricanes, typhoons, etc.) and seeing photographs or film footage of the devastation. In this case, we are more inclined to believe what we see. Invariably, however, we often confer validity to a photograph, which may or may not be justified by the circumstances.

Our penchant for investing evidentiary weight into what we see carries over into other realms, including viewing images associated with medical tests and procedures. For instance, an x-ray of a hairline fracture can provide the documentary evidence of an injury sustained in a fall – an injury that might not be obvious absent that imaging. But unlike x-rays, the images from which are relatively straightforward given even a rudimentary understanding of human anatomy, brain imaging (i.e., fMRI, SPECT, and PET) presents a host of challenges and idiosyncrasies that defy simple extrapolation.

With respect to fMRI, while the final images produced may resemble a photograph (especially to the uninitiated), they are not photographs. In fact, the data garnered through fMRI are far removed from final image of an object that looks like a brain with variously colored blotches. One commentator refers to this as "inferential distance" –

[1]Interestingly, from the beginning of photography, manipulation of images, either through technical means or through the staging of a photo's subject, was also a part of the craft of photography. For instance, U.S. Civil War photographer Matthew T. Brady occasionally rearranged dead soldiers' bodies on the battlefield for his photos, either for a more dramatic effect or for a more cohesive visual narrative of the nature of the war.

the difference between the image resulting from the fMRI and the neural activity from which the image is constructed (Roskies, 2008). Because fMRI images retain basic spatial information, and show some structures of the brain, if only in a rudimentary way, fMRI images may be assumed to be as evidentiary as photographs. Certainly the public and the media are unlikely to appreciate that fMRI is the result of correlates of neural activity, blood oxygenation levels, and statistical calculations. For the most part, they are inclined to see the brain-like image and attach the same credibility they would to a photograph. This inclination is reinforced by popular media, where fMRI has been portrayed as a "real time" process on at least one popular U.S. television show.

An additional potential complication to public understanding of fMRI comes from an interesting study conducted in 2008, which sought to demonstrate what the authors referred to as the "allure of neuroscience explanations" (Weisberg et al, 2008). The study found that non-experts in neuroscience (i.e., the lay public and students in an introductory neuroscience course) were more satisfied with explanations of psychological phenomena when they contained logically irrelevant neuroscience information than they were by the same explanations absent that irrelevant neuroscience information. This phenomenon suggests that persons who have limited understanding of neuroscience may well be more vulnerable to arguments that rely on these types of explanations when deciding whether to participate in research or undergo clinical procedures.

Limited public understanding of the process of producing neuroimages partly underlies another trend: commercializing neuroimaging scanning. While most of these operations (in the U.S.) involve single-photon emission computed tomography (SPECT), there are a few relying on fMRI, which purport to be the next generation of lie detectors. These companies all rely on the power of images to draw in potential customers. Used in a courtroom proceeding, a "photograph" of a brain with brightly colored spots that claim to represent a diagnosis, a proclivity, or a prediction of some aberrant behaviour could be more compelling than oral testimony. In popular culture, the entire notion of marketing and advertising are predicated on the power of images (and words) to persuade people to behave in the desired way – i.e., to purchase a specific product or service. Indeed, the relatively new field of neuromarketing is a testament to the strength of the association, and to deterministic thinking.

2.8.1 Recommendations

- The neuroscience community, science communicators in general and the media have an ethical responsibility to be mindful of the fact that the lay public will attach a lot of power to the images resulting from fMRI. The misunderstanding of what these images represent can inevitably lead to misuse of these images.

- The use of fMRI, particularly outside neuroclinical or neuroscientific environments, including other areas of scientific research, marketing, legal, employment, education, and military, where misinterpretation and over-interpretation of fMRI brain images is more likely to happen, should always be supported by objective neuroscience.

- In some situations the power of fMRI images may be responsibly used, for example in explaining diagnosis or prognosis in the context of psychiatric or neurodegenerative diseases or in planning a brain intervention (Farah and Gillihan, 2012).

- It is important to always bear in mind that fMRI is not intended as a standalone technique, whether in use in research, in the clinic, or beyond.

- It is a responsibility of scientists to clearly explain not only fMRI findings, but also the conventions and the meaning of fMRI brain images, the methodology behind the study and its limitations and societal impact of research. Sometimes statistical brain maps are not the best method to represent fMRI results, and the most appropriate science representation method should be chosen over the most appealing (Logothetis, 2008).

- Science communication and techniques of representation of fMRI results should be part of the curricula of fMRI teaching programmes.

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