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# History and future directions of human brain mapping and functional neuroimaging

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## Abstract

It has long been known that there is some degree of localisation of function in the human brain, as indicated by the effects of traumatic head injury. Work in the middle of the 20th century, notably the direct cortical stimulation of patients during neurosurgery, suggested that the degree and specificity of such localisation of function were far greater than had earlier been imagined. One problem with the data based on lesions and direct stimulation was that the work depended on the study of what were, by definition, damaged brains. During the second half of the 20th century, a collection of relatively non-invasive tools for assessing and localising human brain function in healthy volunteers has led to an explosion of research in what is often termed “Brain Mapping”. The present article reviews some of the history associated with these tools, but emphasises the current state of development with speculation about the future. © 2001 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

Let me begin by defining three terms: psychology, neuropsychology, and brain mapping. The first definition that I learned in college was for the term *psychology*: “The science that attempts to understand (i.e., explain, predict, and control) beha-

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viour.” This definition was stated by Professor Hans-Lukas Teuber (the founder and then Chair of the Psychology Department at the Massachusetts Institute of Technology) to contrast it with the enterprise that most interested him: *neuropsychology*: “The science that attempts to understand the interactions between the nervous system and behaviour.” The distinction between psychology and neuropsychology (i.e., the distinction between behaviour and physiology) is another way of thinking about the question which the authors of this special issue of *Acta Psychologica* have been asked to address: “What is the role of traditional Psychonomics in the broader enterprise that goes by the name Cognitive Neuroscience?” This is a question of current interest and excitement primarily because of the explosion of research in *brain mapping*: the attempt to specify in as much detail as possible the localisation of function in the human brain. The growth of this research is driven largely by new developments in a collection of non-invasive technologies, with increasing spatial and temporal resolutions. Questions and opportunities are implied by this work for us as psychologists. Can our expertise in the study of behaviour improve the enterprise of brain mapping and, more generally, cognitive neuroscience? Do the new discoveries about human brain function based on neuroimaging experiments really teach us things that are relevant for the study and understanding of behaviour?

You will judge for yourself the answers to the above two questions by reading the collection of articles – addressing specific scientific applications – that compose the bulk of this special issue of *Acta Psychologica*. The present article will present an overview of the tools of functional neuroimaging, with a mildly historical flavour and an emphasis on the past, current, and future spatial and temporal resolutions of the relevant technologies. There will be an emphasis on functional magnetic resonance imaging (fMRI) because it is, in many ways, the most exciting new volumetric imaging tool, and (not coincidentally) because the experiments in this special issue are mostly based on fMRI.

It is important to note that the enterprise of brain mapping did not begin with fMRI or any other non-invasive imaging tool. The understanding that localisation of function is pervasive in the human brain has been well established for more than 50 years. Consider, for example, the summary of this knowledge represented by Fig. 1, reproduced from a book published in 1957 (Polyak, 1957). There are at least two kinds of questions that should be asked about this figure. The first questions are methodological: What is the basis for this figure? Where did the data come from? What were the technologies that gave rise to this data? The answer to these first questions is that the figure is based upon two techniques: study of people with lesions (caused, for example, by stroke, disease or traumatic wounds) and the direct electrical stimulation of the cortex of patients undergoing brain surgery. More about these techniques will be written below.

The second question that should be asked about Fig. 1 is: “What is the status of the data in terms of our current knowledge of the localisation of human brain function?” In other words, is the information portrayed in the figure accurate, as far as we know today? The answer, perhaps surprisingly, is that this figure is remarkably accurate. There is nothing indicated in the figure that is obviously wrong (though some of the terminology is out-of-date). On the other hand, as will be apparent in the

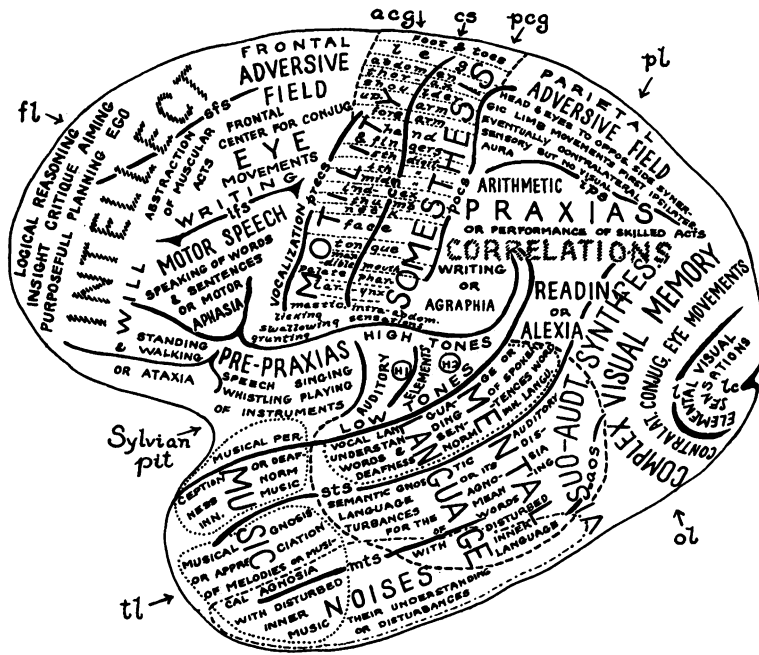


Fig. 1. This figure schematically summarises the state of knowledge of localisation of human functional brain in 1957. It is based on data from lesions and studies using direct cortical stimulation during neurosurgery. (Reproduced with permission from the publisher from Fig. #275, p. 456 of "The Vertebrate Visual System", by Stephen Polyak).

remainder of the articles in this special issue of *Acta Psychologica*, a great deal more is known about the localisation of function in some areas (perhaps most notably in the multiple visual areas of the occipital lobe), and there are a wide variety of subtle perceptual, cognitive, and emotional tasks that have been used to refine this map at the cortical level, and to add information about subcortical structures, as well.

Thus, Fig. 1 teaches us that we were far from ignorant or misguided about localisation of brain function in 1957. So, what is all the current excitement about? The primary answer<sup>1</sup> is that today there are a host of technologies that can be used to give us information non-invasively that address the same issue. The study of patients

<sup>1</sup> There is a second important difference in the nature of our current knowledge about localisation of function. Fig. 1 represents an informal summary of the "average" information collected across many patients, but this is not a quantitative average of spatial localisation information. One way in which our current knowledge is enriched is by taking advantage of developments for specifying the data for individual subjects in one of a variety of spatially normalised co-ordinate systems (e.g., Talairach proportional co-ordinates for volumetric data (Talairach & Tournoux, 1988), surface-based co-ordinates on a flattened cortical representation (Drury et al., 1996), and co-ordinates presented on inflated cortical surfaces (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). Each of these techniques has its strengths and limitations (which are not the topic of the present paper). The point, however, is that each enables some form of quantitative averaging of the localisation data obtained from the brains of healthy subjects, in marked contrast to the data in Fig. 1.

with lesions, or those who are undergoing direct cortical stimulation during surgery, has substantial limitations. For ethical reasons, neither lesions (obviously) nor direct electrical stimulation of the brain via surgery (for reasons of general risk associated with exposing the brain) may be used in the study of healthy human subjects. Furthermore, the data in Fig. 1 are based on brains that were (by definition) not in a normal state of health.

Today, we have a plethora of techniques that allow us to measure brain function in healthy human subjects of all ages, repeatedly, and safely, over substantial periods of time. Each of these techniques has its own safety considerations, and each has characteristic limits in terms of spatial and temporal resolutions. Nonetheless, they permit us to generate data that are more refined than the information shown in Fig. 1, and which have the promise to become substantially better in the near future.

## **2. History: lesions**

Historically, the oldest data for suggesting localisation of function in the human brain have come from people with lesions caused by disease or trauma. Three famous individuals and a collection of anonymous cases deserve particular mention because of their influence on the understanding of the importance of localisation of human brain function. The first was Phineas Gage. In 1848 he suffered severe (but remarkably localised) damage to his frontal lobes in an industrial accident. While he retained much of his original intelligence, his personality was dramatically and permanently altered. Even more influential was “Tan”, Paul Broca’s patient whose damage to left frontal cortex and consequent loss of language skills led the way to our understanding of the localisation of language preferentially to the left hemisphere in most people. Probably the most famous case in the history of memory research is H.M., whose bilateral medial temporal lobectomy in 1953 led to his immediate and permanent global amnesia for new material. All of these cases are documented in standard texts on Neuropsychology (e.g. Kolb & Whishaw, 1996). In addition to these famous patients, there is a group of anonymous individuals whose lesions led to one of the earliest systematic studies of cortical localisation. In the Russo–Japanese war of 1905 rifles were used which, for the first time, fired bullets that moved fast enough to enter and exit the brains of victims cleanly, often leaving well-defined scotomas in their visual fields, but no other neurological damage. Despite the complications of cortical folds and individual differences, Dr. Inouye (cited in Polyak, 1957), painstakingly reconstructed the paths of the projectiles and correlated these with the scotomas to conclude that there was a retinotopic map in the visual cortex that followed the spatial regularity of the visual world. Modern studies with monkeys and even more recent neuroimaging studies with humans have elaborated this idea most dramatically, with the demonstration of multiple visual areas in human occipital cortex all based on the systematic spatial representations of the visual world (e.g., Tootell, Dale, Sereno, & Malach, 1996).

Evidence from patients continues to be a source of important information for brain mapping. Moreover, the use of structural Magnetic Resonance Imaging to give

us much better information about the extent of damage due to disease, trauma or surgery makes the associated behavioural data from patients much more valuable for ongoing scientific study. Even famous historical (but still living) patients like H.M., most of whose behavioural data were collected with only limited knowledge of the exact location of the lesions, are better understood now because we have MR images of his brain (Corkin, Amaral, Johnson, & Hyman, 1997).

### **3. History: direct stimulation of exposed cortical tissue**

The work of Wilder Penfield and colleagues in the middle of the 20th century revolutionised our understanding of cortical localisation (Penfield & Jasper, 1954). Given antiseptic techniques that permitted the relatively safe exposure of the brain for substantial periods of time during surgery, and given the need to attempt to avoid particularly critical areas of the brain (having to do with language and/or motor control) even when some tissue needed to be removed for clinical reasons, it was natural to use direct cortical stimulation of the patient's brain to map function. Indeed, this work was the basis for much of the information in Fig. 1. Today, direct cortical stimulation during surgery is still widely used for the same reasons. An excellent and engagingly readable summary of the modern version of this enterprise can be found in the book *Conversations with Neil's Brain* (Calvin & Ojemann, 1995).

### **4. Modern brain mapping: intra-cranial recordings and stimulation**

In addition to the use of cortical stimulation *during* surgery, there is another form of direct cortical recording and stimulation that is sometimes used *prior* to the ablative surgery. This is the technique of subdural and/or intra-cortical electrodes, in which one or more strips of recording electrodes are placed directly into the patient's brain. The usual clinical need for such recording is driven by the desire to specify the foci of epileptic seizures. The neurosurgeon and neurologist specify the region of the brain that is, in their opinions, most likely to contain the foci for the seizures, and patients have strips of electrodes implanted in their brains for a period of time (from a few days to several weeks) during which the activity in these areas is recorded between and during seizures. It is also possible to stimulate the brain using the same electrodes (for example, to see if such localised stimulation triggers an aura or a seizure). An obvious limitation of such work is that the placement of the electrodes is driven by the clinical needs of the patient, and not by the research interests of the brain mapper. Because the temporal lobe is often the focus of debilitating cases of epilepsy, most such studies have used electrodes in that location. However, there is the occasional need for placing electrodes elsewhere in the brain, and the alert brain mapping collaborator can take advantage of those cases. Much of this work is necessarily of a "case study" type (e.g., Halgren, Walter, Cherlow, & Crandall, 1978; Vignal, Chauvel, & Halgren, 2000), but some of these direct (albeit invasive)

electrical measurements have lent systematic support to the belief in the validity of some of the less invasive methods, such as fMRI (Puce et al., 1995).

## 5. Modern brain mapping: temporary lesions and stimulation via TMS and TES

The above method for recording and/or stimulating the brain requires surgery and is, therefore, highly invasive. There are now at least two techniques for cortical stimulation of healthy human subjects that do not involve surgery. The first is transcranial magnetic stimulation (TMS). In TMS, a coil (or a pair of coils forming a figure-8) is placed near the subject's head and a very brief, very large pulse of current is run through it. This creates a strong, transient magnetic field. The transient magnetic field can induce current flow nearby conductors, such as the neurons inside the brain. The other technique is called transcranial electrical stimulation (TES). In TES electrodes are placed on the head and current is run between the electrodes (Brandt et al., 1999). The electrodes are far enough apart that some current flows through the brain (as well as the scalp). Because TES uses electrodes on the surface of the head and causes current to run through the skin (on the way to the brain), it necessarily causes some pain and has been less extensively studied than TMS to date. While TMS can also cause some direct physical discomfort (typically by exciting muscles in the head or face), TMS often has no directly unpleasant effects, other than the noise that it makes during stimulation. The following comments, therefore, emphasise TMS, rather than TES.

TMS is a potentially useful investigative tool because of two effects. First, it can cause "activation", as indicated by the response of peripheral muscles after stimulation of primary motor cortex. Second, it can cause "temporary lesions" by disrupting normal activity in a localised region of the brain. Thus, TMS has the potential to simulate in normal subjects both of the critical forms of information (lesions and direct cortical stimulation) that gave rise to Fig. 1. From a theoretical perspective, this is very important. One of the constant concerns about any of the other brain mapping techniques is that they may be interpreted as revealing only what is incidentally active during some task, rather than what is essential for the performance of that task. Only a technique which disrupts the activity of some part of the brain can be used to show that that part is necessary for the behaviour, rather than just incidental to it. For these (and other) reasons, TMS is becoming a more widely used technique in functional brain mapping. (For general introductions, see, e.g., Pascual-Leone, Bartres-Faz, & Keenan, 1999; Pascual-Leone, Walsh, & Rothwell, 2000; Stewart, Ellison, Walsh, & Cowey, 2001; Walsh & Cowey, 1998); for a special journal issue devoted to TMS, see Pascual-Leone & Meador, 1998, and for focus on clinical applications see George, Lisanby, & Sackeim, 1999).

This argument in favour of the use of TMS for brain mapping must be balanced by some of the limitations of TMS. The two biggest concerns are safety and spatial resolution. Safety is less of an issue when individual TMS stimulations are well separated in time (e.g., more than 1 s apart). On the other hand, when stimulations are presented repeatedly (so-called "repetitive TMS" or rTMS) at a rate of 5–10

pulses per second, seizures can be induced in normal subjects. The parameters for safe use of TMS have been studied (see, e.g., “Box 3” in Walsh & Cowey, 1998), but this issue is always a concern. On the other hand, the fact that rTMS can induce seizures may be related to reports of possible therapeutic effect in contexts where it does not induce seizures. Repetitive TMS has been studied as a more benign but possibly effective alternative to electroconvulsive therapy (ECT) in the treatment of severe depression (e.g., Pascual-Leone et al., 1998), but the results are not yet conclusive (George et al., 1999).

The other significant concern with TMS (relative some other brain mapping methodologies) is limited spatial resolution. The depth and spatial extent of the areas affected by TMS are hard to specify and are certainly not small (Pascual-Leone et al., 1999) and the precision with which these activation extents can be specified is currently undefined. While some evidence suggests a peak focal activity in the 0.5–1.0 cm range, this is misleading for at least two reasons. First, it is not clear how much activation is elicited directly by the fringe fields that are farther from the peak; and second, it is almost certain some of the effects are propagated by the axons themselves, so that more peripheral brain regions will be influenced. Furthermore, while the temporal precision of the electromagnetic stimulus is excellent (measured in microseconds), the temporal duration of the effective stimulation and/or disruption caused by TMS is less easy to prescribe.

TMS is clearly a tool that is valuable in its own right (see, for example, Stewart et al., 2001). Even more exciting, however, is the integration of TMS with the other tools of anatomical and functional neuroimaging (Foltys et al., 2000; Paus, 1999; Paus & Wolforth, 1998).

## **6. Modern brain mapping: electromagnetic recording**

There are two technologies for non-invasively recording the electrical activity of the human brain: electroencephalography (EEG), and magnetoencephalography (MEG). Both are exceptionally safe and both have millisecond temporal resolution. Both can be used to measure electrical activity continuously (so-called “brain waves”), or to obtain repeated responses to a fixed type of stimulus and average the results (so-called “event-related potentials” – ERPs from EEG; or “event-related fields” – ERFs from MEG) which is the way they are normally used in brain mapping research and cognitive neuroscience. On the other hand, both are limited in terms of volumetric spatial resolution because they can only measure signals outside the surface of the head. Interpreting surface data as representing point sources or a distribution of activity volumetrically within the brain is one of the challenges of EEG and MEG data analysis. The primary way in which this issue is being currently addressed is to combine EEG and MEG data with volumetric anatomical and functional data, largely from MRI (e.g., Dale et al., 2000; Dale & Sereno, 1993).

The history of EEG is extensive, and is well summarised in a variety of sources (Brazier, 1961, 1988; Swartz & Goldensohn, 1998). MEG is a much more recent development, based, as it is, on the technology of superconducting, quantum

interference devices<sup>2</sup> (SQUIDs) (Clarke, 1994). SQUIDs permit the detection of tiny (femtotesla, fT) magnetic field gradients. They are used to detect the magnetic field gradients generated outside the skull by cortical currents. Various reviews are available for general information about EEG (Gevins, 1996; Lewine & Orrison, 1995a) and MEG (Lewine & Orrison, 1995b; Lounasmaa, Hämäläinen, Hari, & Salmelin, 1996), with an emphasis on their use in localisation of function.

EEG and MEG share the strengths of excellent temporal resolution and safety. They share the weakness of poor three-dimensional spatial localisation, because any volumetric localisation within the head has to be generated based on data collected at or just outside the scalp (the “inverse problem”), and this is a mathematically ill-posed problem. It has been suggested that MEG and EEG detect signals that tend to come from electromagnetic sources of different physical orientation in the brain, and are therefore potentially complementary, with the inverse problem for MEG being somewhat more tractable (Lounasmaa et al., 1996), but this assertion has come into question and some people believe that EEG and MEG measure very similar signal sources. Both technologies have been developed to include large arrays of sensors. The major differences, in practical terms, are that MEG machines are much more expensive and are, therefore, much less readily available to psychological researchers, while EEG can be cumbersome to use because of the need to attach many electrodes to the scalp. Recent development of nets containing many sensors has made high-density EEG recording more practical.

EEG has been used extensively in clinical applications. It is a major diagnostic tool in neurological disorders. Because of its exquisite temporal resolution, it can be used, for example, to detect specific lesions in the auditory pathway that are characterised by eight different peaks in electrical activity that all occur within 10 ms of stimulus onset (e.g., Adams & Victor, 1985). This kind of temporal resolution is unthinkable in the context of hemodynamically based functional neuroimaging (below). However, as noted above and as will be elaborated in a later section, one of the most exciting potential areas in functional neuroimaging is the integration of the high temporal resolution electrical tools with the higher spatial resolution volumetric imaging tools such as MRI and fMRI.

## 7. Modern brain mapping tools: hemodynamic responses to neural activity

All of the preceding technologies have measured some aspect of the electromagnetic activity of neurons directly. As such, they have had temporal resolutions based on either the technology itself (typically milliseconds or better) or the neural response (also on the order of milliseconds). There is another collection of tools that can be

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<sup>2</sup> This technology is the descendant of three Nobel-prize-winning works of physics awarded in 1913, 1972, and 1973, based on work performed in 1911 (the discovery of superconductivity), 1957 (the theory that explains superconductivity), and 1962 (the theoretical prediction of what is now called the “Josephson Junction”).



used to investigate human brain function based on a more indirect measure: the changes in blood flow and the changes in venous oxygenation level that follow neural activity. Collectively, these are referred to as “hemodynamic” changes, and they are the source of virtually all volumetric functional brain imaging data in healthy humans.

There is a recently written history of the development of these technologies available in journal form (Raichle, 1998) or, more extensively, in a book chapter (Raichle, 2000). Work with human patients (Fulton, 1928; Mosso, 1881) hinted strongly that there was a connection between local cerebral hemodynamics and neural activity. But it was the work with animals (Roy & Sherrington, 1890), using the exposed brain of a dog, that gave the first clear, quantitative demonstration that local cerebral blood volume changed as a function of cortical activity. The development of technologies that could measure these changes safely in normal human subjects would take another 100 years. One of those technologies (positron emission tomography (PET) described below) led to the discovery that the increase in blood flow triggered by neural activity was not matched by an equal increase in oxygen utilisation (Fox & Raichle, 1986). This mismatch (substantial increase in flow rate, but minimal increase in oxygen use) causes a decrease in the concentration of deoxyhemoglobin in the venous side of the circulation near regions of neural activity. Deoxyhemoglobin is paramagnetic and distorts the local magnetic field. Thus, the changes described above can be detected using Magnetic Resonance Imaging. Finally, there are a host of optical parameters (e.g., the differences in reflectance and absorption spectra of hemoglobin and deoxyhemoglobin) that can be used to detect changes in blood flow and oxygenation. While these are most well known in the context of invasive procedures (exposing the cortex and blood supply of the brain), they are starting to be exploited non-invasively (Gratton & Fabiani, 1998; Gratton, Maier, Fabiani, Mantulin, & Gratton, 1994; Villringer & Chance, 1997).

## 8. Modern brain mapping: hemodynamics via PET

Position emission tomography is based on the decay of radioactive atoms that release positrons. Each positron annihilates a nearby electron and the annihilation results in the release of a pair of oppositely directed high-energy gamma rays. The coincident detection of this pair of gamma rays on opposite sides of the head – thus defining a line along which is the likely source of the gamma rays – forms the basic data for PET. For functional neuroimaging, the radioactive atom of choice is oxygen-15.  $O^{15}$  has a half-life of about 2 min, so it only takes 10 min for almost all of it to have decayed after administration. It is administered either by breathing air containing  $O^{15}$  in  $CO_2$ , or by injecting water ( $H_2O$ ) that has had  $O^{15}$  bubbled through it so that many of the water molecules are now  $H_2O^{15}$ .

PET has been an important tool in the mapping of all aspects of the physiology of brain function – not just neural activation. Glucose metabolism, Krebs

cycle function, protein synthesis, dopamine receptors, and DNA replication are just a few of the biological functions studied using PET. Blood flow, blood volume, and oxygen utilisation have been studied quantitatively with PET, in the context of the hemodynamic changes associated with neural activity in the human brain, in a way that is not yet possible with any other modality. For a good general introduction to the technology and applications, see, for example, Cherry and Phelps (1996).

From the perspective of a psychologist, however, PET has three limitations that impact directly on experimental design. First, it uses ionising radiation, so the number of times a given subject can be scanned in any one year is limited by governmental (and ethical) considerations. Governmental guidelines limit the total radiation dose per year per volunteer subject. As scanners have been made more sensitive, it is possible to get useful images from smaller doses, and hence the number of images available per subject has increased. For modern PET scanners using  $O^{15}$ , this number is as high as 32 separate images. The second limitation is spatial resolution. One cubic centimeter is a good rough estimate of the best that PET is likely to yield. Finally, and most importantly from the perspective of experimental design, the process of PET imaging for cognitive function assumes that the brain (and blood flow to the brain) are in a “steady-state” condition for a period of 30–90 s as radiation counts are collected for a single image. Thus, in a typical PET  $O^{15}$  cognitive study, one image is collected every 10 min, and the subject must be performing the same task for a substantial period of time – typically about 30 s before and 60 s during – data collection. Generically, the resulting experimental designs are called “block” designs, because each experimental condition is established by many similar stimuli over a substantial block of time.

The above three issues have always been limitations for cognitive studies using PET. Nevertheless, classic work (e.g., Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Petersen, Fox, Posner, Minton, & Raichle, 1988) in cognitive neuroscience has been accomplished using PET and block-design experiments. However, the advent of fMRI has largely replaced PET as the primary tool for volumetric functional neuroimaging. While fMRI has its own problems, it does represent very significant improvement relative to the three limitations mentioned above for PET.

PET will continue to be an important tool in neuroscience for several reasons. One of the most important is the flexibility in its choice of chemical marker (e.g., including neurotransmitters). Another is its sensitivity – virtually every radioactive decay event is detected. These two strengths are likely to be of particular importance in future animal studies, and may be crucial in the ultimate unravelling of the mysteries of the biophysics underlying the neurally triggered hemodynamic responses. From the perspective of psychology and the context of human functional neuroimaging, there is one further strength of PET, especially as compared with fMRI. The physical and psychophysical environment of the PET scanner is relatively friendly: claustrophobia is almost never a problem and there is no acoustic noise – both in marked contrast to the environment of MR imaging.

## 9. Modern brain mapping: hemodynamics via functional MRI

Functional <sup>3</sup> MRI refers, in the present context, to the detection of hemodynamic changes associated with neural activity, using the technology of MRI. It represents a novel application of a tool that was developed to create images of the soft tissue of the body while avoiding the ionising radiation used, for example, in X-ray images. Structural MRI has revolutionised medical diagnosis, making this tool a virtual necessity in most clinical settings. The resulting availability of MRI machines in many hospitals and research laboratories around the world made it a particularly appealing tool for functional brain mapping when the appropriate means of applying it were developed. In turn, the success of fMRI as a brain mapping tool and potential clinical tool has fostered the development of advances in MRI, and particularly the development of higher field MRI machines (3 and 4 T, rather than the standard clinical 1.5 T) by commercial manufacturers.

### 9.1. *The basic physics of NMR, MRI and fMRI*

The physical principle underlying magnetic resonance imaging (MRI) is nuclear magnetic resonance (NMR). Various magnetic fields are used to generate the NMR signal from the hydrogen nuclei of water molecules in the body. Other magnetic fields are used to elicit distinguishable NMR signals from various positions in the three-dimensional space of the body, thus permitting the creation of a volumetric image – MRI. The term “pulse sequence” refers to the temporal and intensity pattern of the various electromagnetic sources and sensors used in the MRI device. Specific pulse sequences can be used to generate images that indicate the hemodynamic changes associated with neural activation – fMRI.

The technology for creating images in MRI is very flexible, and too intricate for explication in the present context (see Bushong, 1995, for a complete introduction), and even the specifics of its application to functional MRI warrant a lengthy explanation (Bandettini, Birn, & Donahue, 2000) with advanced fMRI applications requiring a book (Moonen & Bandettini, 1999). However, a few general points should be mentioned.

First, images of the brain can be collected rapidly. A single slice of the brain can be imaged at  $3 \times 3 \text{ mm}^2$  in-plane resolution in less than 50 ms. Whole brain imaging in 2–3 s is routine. (There is always a trade-off between imaging time, spatial resolution, and signal-to-noise in MRI.)

Second, functional MRI refers to two different techniques for studying the hemodynamics associated with neural activation. One technique looks at blood flow directly. Various pulse sequences can be applied so that the resulting images are sensitive to flowing blood. By varying the imaging parameters, the images can be

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<sup>3</sup> “Functional MRI” can, in other contexts, refer to any use of MR imaging to study function in the human body. The use of the name functional MRI for the study of neural activation is probably unfortunate because it is ambiguous, but other candidate names – such as neural functional MRI (NFMRI or NMRI) – have not caught on.

made preferentially sensitive to fast-flowing blood or to slow-moving blood. In both cases, this is normally arterial blood, with fast-flowing blood generally found in larger arteries, and changes in flow rate (across images collected at different times) being the indicator of nearby neural activity. People who study these changes in sensitivity in detail note that, by choosing a flow rate, one may be able to increase the spatial specificity of the activation, with slower arterial rates corresponding to smaller vessels, which are presumably closer to the site of neural activity (Bandettini et al., 2000). The second technique makes use of the fact (as mentioned above) that despite the substantial increase in blood flow after neural activity, there is a much smaller increase in oxygen utilisation. This leads to a decrease in the concentration of deoxygenated hemoglobin in the venous blood, and because deoxygenated hemoglobin is paramagnetic, this also leads to a decrease in the local distortion of the magnetic field. These changes are sometimes called the blood oxygen level dependent (BOLD) effect, and constitute the main mechanism used for detecting the hemodynamic changes induced by neural activity in fMRI-based research. (Historically, the first experiments using the BOLD effect with humans were reported in Kwong et al., 1992, which incidentally also included flow-based effects, but the background developments are considerable and are well summarised in Raichle, 2000.)

By rapidly changing the imaging parameters, it is even possible to collect alternate images of each type (based on flow or BOLD) every few seconds (Wong & Bandettini, 1999). Such fancy imaging protocols may be of relevance when designing studies that attempt to gain very high spatial or temporal resolution with fMRI (Kim, Lee, Goodyear, & Silva, 1999) and when attempting to refine our characterisation of the biophysics of these hemodynamic effects. However, they are not presently needed in routine cognitive studies.

The third general observation about fMRI that should be mentioned is that it is a technology which is still in the process of rapid improvement, in part because of work at higher magnetic fields. Why is the use of high fields so important? Generation of the NMR signal begins by using a strong, spatially uniform magnetic field to align a significant fraction of the atomic nuclei in the target object (or person). Only those nuclei that possess a magnetic moment will be influenced by the magnetic field. Fortunately, the hydrogen nucleus has the largest magnetic moment of any atom and is also the most abundant in the body. Nonetheless, in a 1.5 T magnet, only 1 out of each 100,000 hydrogen nuclei aligns itself with the applied magnetic field. (This fraction is so low because the magnetic field of the nucleus is so tiny that the magnetic coupling between the external field and the nucleus is very weak compared to thermal fluctuations of the nucleus.) This is a small fraction, but it still represents a large number of nuclei. It is the macroscopically observable magnetic field of this collection of commonly oriented nuclei that gives rise to the NMR signal. One of the ways to increase the power of the tool is to increase the strength of the main magnet. Signal strength goes up as the square of the field (while noise only goes up linearly). Obtaining greater signal strength for fMRI is one of the motivations for the ongoing development of MRI at higher fields (such as 3, 4, and even 7, or 8 T). As will be apparent in some of the observations below, higher fields are very relevant for improving the spatial resolution of fMRI, and may even help with the temporal res-

olution, by enabling the detection of different phases of the hemodynamic response to neural activity. On the other hand, the technical challenges of working at higher fields are substantial. These include the dangers of high intensity acoustic noise as well as the greater sensitivity to non-uniformities in the magnetic field (so-called “susceptibility artefacts”). But the potential rewards for working at higher fields are great, so the efforts continue.

## 9.2. *fMRI and experimental design*

How do the technology of MRI and the underlying hemodynamics of the brain lead to improvements in the three limitations described above for PET? First, eliciting an NMR signal from the body does not require the use of ionising radiation. At 1.5 T, it is considered safe<sup>4</sup> to collect an unlimited number of images of an individual subject, including children volunteers. Thus, it is possible to collect a vast amount of data, covering a wide range of experimental tasks, from a single subject.

Second, the spatial resolution of fMRI is substantially better than that of PET. It is hard to specify an exact number that applies across all conditions, but even with conventional 1.5 T MRI systems, common imaging parameters are  $5 \times 5 \times 5 \text{ mm}^3$  isotropic voxels or  $3 \times 3 \text{ mm}^2$  in-plane resolution with a slice thickness of 7–8 mm, yielding an effective volume resolution of about 0.1 cubic cm. Using higher magnetic fields (e.g., the 3 and 4 T systems that are available at a limited, but rapidly growing number of research institutions), it is possible to conduct functional imaging at substantially greater spatial resolution. Early reports of the detection of visual ocular dominance columns using fMRI (Menon, Ogawa, Strupp, & Urgurbil, 1997) have been confirmed in a particularly elegant imaging study by Kang Cheng (Cheng, Waggoner, & Tanaka, 1999). Both of these studies used 4 T MRI devices and claimed an effective in-plane resolution of approximately 600  $\mu\text{m}$ .

It is not clear whether the ultimate limits to spatial resolution in human fMRI will come from practical limits of the imaging device, or from the underlying physiology of the blood circulation. Current estimates of the latter resolution are about  $1 \text{ mm}^3$  ( $0.001 \text{ cm}^3$ ), as determined by the size of arterioles that supply the capillary bed, but there is also a possibility that the capillaries themselves might have hemodynamic properties, in which case the ultimate spatial resolution based on hemodynamics might be even smaller (Villringer, 1999). Moreover, in-plane resolution as low as 0.1 mm has been demonstrated for invasive optical imaging with cats and monkeys (Frostig, Lieke, Ts'o, & Grinvald, 1990).

The question is not whether fMRI could, in terms of the fundamental physics of MR imaging, obtain such resolution. Rather, the limits would almost certainly be imposed by practical problems such as subject movement (both of the head, and even of the brain due to arterial pulsations if the skull were immobile) and the amount of time needed to collect such high-resolution images. While higher field strengths (in

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<sup>4</sup> Higher field (3 T) machines have recently been approved for clinical use in the United States, and the experimental use of 4–8 T whole body MRI machines has been approved for humans.

terms of both the main magnet and the gradient magnets used for imaging) permit faster imaging – and therefore less susceptibility to motion artefacts – both cost and safety considerations may set the practical limits of the spatial resolution of fMRI.

The third improvement in experimental design offered by fMRI (in addition to being able to run subjects many times, and having better spatial resolution), is a dramatic increase in the effective temporal resolution. While the temporal resolution is not likely to approach those systems that are based on the electromagnetic signals from neurons (e.g., EEG and MEG, discussed above), nor the optical systems (described below), the increase in temporal resolution relative to the other volumetric imaging tool (PET) is very important for improving the flexibility and power of experimental design (Rosen, Buckner, & Dale, 1998).

Early demonstrations of the detection of very brief visual stimuli (Savoy et al., 1995; Savoy et al., 1994) were followed by the demonstration that randomly sequenced cognitive trials could be pooled to yield measurable fMRI signal differences (Buckner et al., 1996). In the latter study, brief stimuli were spaced well apart (e.g., one every 16 s) so that the hemodynamic response to the individual stimuli and cognitive response had time to rise and fall back to baseline levels.

Fig. 2 can be thought of as characterising a typical hemodynamic response to a 1-s stimulus, as detected by fMRI. The MR signal starts to rise about 2 s after the onset of the stimulus, peaks 4–6 s after the onset of the stimulus, and returns to baseline by 10–14 s after the onset of the stimulus. While this is a good general idea, it should be noted that this picture is oversimplified in several ways. First, there is evidence (Hu, Yacoub, Le, Cohen, & Ugurbil, 1999) that there is a more rapid change, with onset latency of less than a second, that results in an oppositely directed MR signal change. This so-called “initial dip” is normally seen using MRI only with higher magnets (e.g., 4 T), but it is consistent with hemodynamic changes detected in animals using optical imaging (Malonek & Grinvald, 1996). In the future, it may serve as a marker that will yield even greater spatial and temporal resolution with fMRI. For the present, however, it is not used in the design of routine fMRI-based experiments in cognitive psychology, both because it requires high field MRI and because there is less power in the initial dip than in the BOLD signal. The phrase “returns to baseline” is also a simplification. The physiological processes by which the venous hemodynamics return to the unactivated state is complicated and there are probably effects that last longer than 14 s (as in the so-called “post-stimulus undershoot” seen in some fMRI data; Buxton, Wong, & Frank, 1999). Finally, there is evidence for considerable variability in the temporal characteristics of these hemodynamic responses across location in the brain (Schacter, Buckner, Koutstaal, Dale, & Rosen, 1997) and across subjects (Aguirre, Zarahn, & D’Esposito, 1998). Nonetheless, for the purposes of experimental design, the picture presented in Fig. 2 might be considered typical.

The study mentioned above (Buckner et al., 1996) takes advantage of knowledge of this kind of temporal response and is an example of what might be called “spaced single trials”. Individual trials are spaced apart, so that most of the hemodynamic response (and the resulting detection by MRI) has ended by the time the next trial begins. This method permits the random arrangement of different trial types, rather

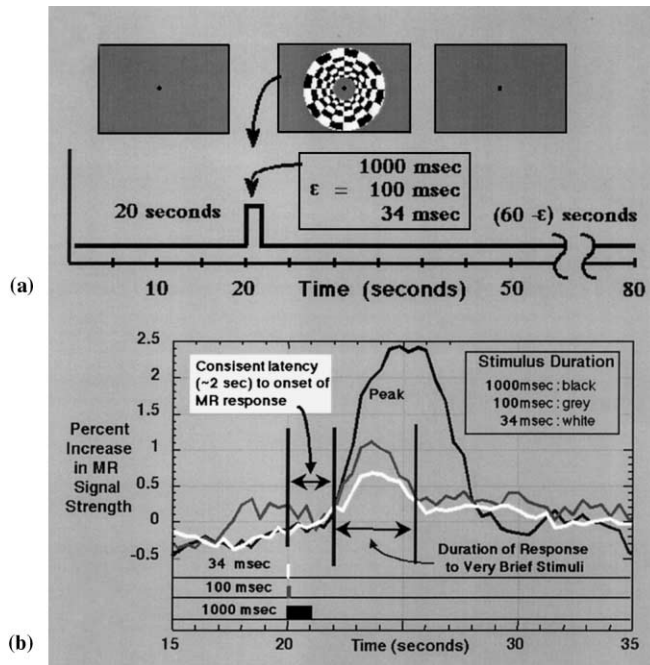


Fig. 2. This figure summarises the results of an early fMRI-based experiment designed to see if a measurable response to very brief stimuli could be obtained (Savoy et al., 1994). The time course of stimulus presentation is indicated in (a). Subjects viewed a blank screen with a central fixation point for 80 s, except for a brief presentation of a high contrast radial checkerboard pattern for 34, 100, or 1000 ms. Data for one subject are shown in (b). These data are based on the average of 10 presentations of each stimulus type, with spatial averaging ("region of interest") over a large portion of visual cortex. It is clear that signal changes are detectable even for the briefest stimulus used. In most practical fMRI-based experiments, stimulus presentation times are usually at least 500–1000 ms.

than the obligatory sequences of similar trials required by the block design. However, the spaced single trial design is somewhat wasteful of imaging time. Many images are collected while the signal returns to baseline. Demonstration of the surprising degree of linearity of the hemodynamic response (Boynton, Engel, Glover, & Heeger, 1996) was followed by the seminal demonstration of Buckner and Dale (Dale & Buckner, 1997) that it is possible to decompose the overlapping hemodynamic responses generated by individual trials placed much closer together than 16 s. This report has led to more efficient and novel experimental designs. The key point of both spaced single trial designs and rapid single trial designs is that several types of stimuli can be presented repeatedly in whatever order the experimenter desires, and the data from each type of stimulus can be averaged together. This yields a volumetric imaging tool that is reminiscent of the ERPs of electrically based tools (EEG and MEG), and, indeed, retains many of the virtues of ERPs – hence the name "event-related fMRI".

Finally, no discussion of the temporal resolution of fMRI would be complete without pointing out that it is possible to see the hemodynamic response to single

trials. The most common way for data to be analysed is by averaging across similar trial types (as in Buckner et al., 1996 above) but the signals generated in many studies (again, especially at high field such as 4 T) are large enough that individual trials can be analysed (e.g., Richter et al., 2000).

### 9.3. *Limitations of fMRI*

While fMRI is clearly a powerful and flexible tool, it is not without dangers and experimental weaknesses. Because MRI is such an important and widely used clinical tool, the potential biological dangers associated with MRI are well documented (Shellock & Kanal, 1996). While MRI is, in general terms, an exceptionally safe technology, it is not without risks. Just being inside a large magnet presents the risk that a careless or untrained individual may bring a magnetic object into the room, with possibly disastrous consequences. There are several problems more specific to functional MRI. For example, (1) the high-speed imaging parameters (e.g., echo planar imaging) that are routinely used in fMRI studies generate a great deal of acoustic noise. While subjects normally use protective earplugs, headphones, and/or padding to protect their ears, the danger is real and it is generally worse with higher field systems (Savoy, Ravicz, & Gollub, 1999). Furthermore, the acoustic noise makes it difficult or impossible to conduct some kinds of auditory experiments. (2) The radio-frequency magnetic field oscillations that are needed to generate the MR signal are non-ionising, but they do generate internal body heat. Governmental guidelines are generally built into the scanner to prevent using imaging parameters that will exceed safe limits. At 1.5 T this is almost never an issue. At higher fields, and for some pulse sequences, it becomes a more serious issue. (3) Related concerns apply to the strong, and rapidly switching magnetic field gradients that are applied during imaging, though the issue in that case is not heat but rather the possibility of inducing direct electrical stimulation (as in TMS, but with cardiac interference being the major concern). Again, there are governmental guidelines indicating safe levels of gradient switching.

In addition to safety considerations, there are practical limitations in MRI-based experiments. The greatly increased spatial resolution is partially mitigated by a greatly increased susceptibility to artefacts induced by subject movement. While this is an issue for any imaging modality, it is probably most critical in fMRI. Thousands of images are collected over a typical 1–2 h scanning session, and these need to be aligned. There are motion-detection and motion-correction algorithms that can be applied to the image data, but the correction algorithms work best if there is minimal motion to begin with. This has led to the development of a number of techniques (from face masks to bite bars to plaster head moulds; Edward et al., 2000) for keeping the subject's head as motionless as comfortably possible, but simply relaxing and using soft pads to wedge the head in place is still probably the most widely used technique (Savoy et al., 1999).

Finally, MR images are strongly influenced by the uniformity of the magnetic field used to generate them. One of the things that can distort the field is having a subject



talk during an experiment. This introduces possible artefacts due to the motion itself, and also due to the creation of different air pockets in the head during speech. In the case of spoken responses that are brief (i.e., shorter than the 2-s delay before the onset of the BOLD signal), it is sometimes still possible to obtain the desired brain images (Birn, Bandettini, Cox, & Shaker, 1999). But many other sources of distortion to the magnetic field, including structures in the head such as the sinuses, cannot be avoided. As a result, it is sometimes necessary to make tradeoffs in image quality as a function of where in the brain one is imaging.

## **10. Modern brain mapping: hemodynamics via optical imaging**

The reflection spectrum of hemoglobin and oxyhemoglobin differ, and this difference can be detected in the visible or near infrared portion of the spectrum. Striking demonstrations of ocular dominance columns and the smaller orientation columns have been obtained using optical imaging of the exposed brains of cats and monkeys (e.g. Bonhoeffer & Grinvald, 1996; Frostig et al., 1990). Moreover, this technique has been used to question some aspects of human functional neuroimaging and to validate others (Malonek & Grinvald, 1996). In short, optical imaging has been a dramatically successful tool in the study of brain function and organisation on the surface of the cortex for animals. As indicated above (in the discussion of the ultimate spatial resolution limits for fMRI) invasive optical imaging yields exquisite spatial resolution. Non-invasive optical imaging is drastically limited by the need to pass light through the material (hair, skin, skull, pia mater, dura mater, etc.) separating the sources and sensors from the vascular surface of the brain.

Nonetheless, it has been natural to ask whether optical techniques can be used for non-invasive functional imaging in humans. A 1997 review (Villringer & Chance, 1997) describes the general issues and opportunities in detail. Using near infrared light, for which the skin and the skull are reasonably transparent, it is possible to obtain data on a variety of biochemical signals (including oxy- and deoxy-hemoglobin) non-invasively. However, the practical use of this technology for cognitive neuroscience is very limited at present. The signals have low spatial resolution and even more limited ability to probe beneath the surface of the cortex. But the fact that optical spectroscopy has the potential to detect the so-called “fast signal” (probably related to changes in the index of refraction at neuronal membranes) which has a potential temporal resolution of milliseconds, means that the rewards for succeeding in the development of such a technology would be great.

Optical imaging continues to be very important for animal studies. And animal studies will probably grow in importance in the context of other imaging modalities (both PET and fMRI) in the future. It is virtually certain that some combination of all three of these modalities, when used with animals and combined with drug studies and single cell recordings, will yield important information about underlying biophysics of the hemodynamic responses to neural activity.

## 11. Current research: excitement; concerns; integrating data

It is impossible to summarise the range of work that has been conducted using the above technologies in the service of brain mapping. An indication of the breadth of this field is apparent, however, by examine the book of abstracts from any of the recent annual International Conferences on the Functional Mapping of the Human Brain (available as supplements to the journal *NeuroImage* in 1996–2000). The Organisation for Human Brain Mapping (OHBM), which sponsors these annual meetings, has received more than 900 abstracts for each of the past 3 years. The abstracts are grouped into such broad categories as: methods, cognition, language, memory, clinical, sensory-motor, brain atlases, etc. One feature of these meetings is that the abstracts are full-page documents, permitting brief sections of each abstract to be devoted to introduction/background, methods, results, conclusions, a figure or two and a few references. In short, the “abstracts” are really minipapers that can give the reader a substantial idea of the nature of current research in brain mapping.

There are many complicated methodological issues in the world of human brain mapping. Indeed, the largest single subset of abstracts from last year’s annual meeting was devoted to “methods”. These concern such questions as: Given the irregularity of cortical size, shape, and foldings, how can we compare brain-mapping data across subjects? Given that MEG and EEG measure electromagnetic signals outside the surface of the skull, and given that this information is known to be mathematically insufficient for specifying the currents and/or magnetic dipoles within the skull, how much localisation of function can we obtain from MEG and EEG alone? Can we combine MEG and EEG data with structural MRI or with other functional data (from PET, fMRI, TMS, etc.) to improve that spatial localisation? Are there mathematical tools to take volumetric functional brain data with temporal resolution limited by the sluggish hemodynamic response and nonetheless derive connectivity information that can have much greater temporal resolution? Can we use MR to image white matter tracts? The list is almost endless.

The remainder of this section will focus on selected subsets of methodological and theoretical issues. First, a set of studies that is exciting because of the essential role that behavioural data played in the design, execution, and interpretation of the functional neuroimaging data will be summarised. Second, limitations inherent in reporting only isolated, activated regions of the brain – often the only data reported in volumetric functional brain mapping (fMRI and PET) will be described. Third, some of the attempts that have been made to go beyond isolated activations will be described.

### 11.1. *Excitement: the role of behavioural data*

The following three sets of studies are particularly relevant to the present issue of *Acta Psychologica* because it was the psychological data, i.e., the behavioural data, that was of critical importance in the design and interpretation of the experiments. The first set concerns memory; the second set concerns visual motion perception and the motion after effect (MAE); and the third set concerns quantifying the brain

activations associated with cocaine use. In all three sets (though in differing ways), analysis of the imaging data depends fundamentally on the behavioural data.

In 1998 a pair of studies from different laboratories was reported together in *Science* (Brewer, Zhao, Desond, Glover, & Gabrieli, 1998; Wagner et al., 1998). The pairing was particularly appropriate. Both studies used functional MRI to look at memory – in one case memory for words, and in the other case memory for pictures. While being scanned, subjects were presented with visual stimuli (words or pictures) and given an irrelevant task to perform. After the imaging portion of the study was over, subjects were given a surprise memory test: A collection of stimuli – some novel and some previously presented while they were in the scanner – was shown to the subjects and they were required to report whether they remembered the stimuli. The behavioural data thus obtained were used to retrospectively group the images collected during the MRI scans. The question was: Did the images collected during trials for which the presented stimuli were subsequently remembered differ in consistent ways from the images collected during trials for which the stimuli were subsequently forgotten? In both experiments (and across a collection of task designs including blocked, spaced single trial, and rapid single trial), there were consistent activations. These were reported by the authors as “predicting” which stimuli were likely to have been remembered. The use of the word “predict” in this context is perhaps problematical: ideally, there should be a replication of these experiments in which the imaging data are used to predict the behavioural data, rather than the behavioural data being used to analyse the imaging data in order to make the claim that they might have been predictable. Nonetheless, these studies are a good example of the interaction between behavioural and imaging experiments and a possible model for future studies in which behaviour is genuinely predicted by imaging.

The motion after effect (MAE) is perennial favourite for fans of visual illusions (see also Culham, He, Dukelow, & Verstraten, 2001). It intruded on some early studies of visual motion processing using fMRI and led to an elegant study by Roger Tootell and colleagues (Tootell et al., 1995) which was reasonably conclusive in demonstrating that the MT/V5 visual processing area was involved in the MAE. But that was not the end of the story. In an elegant commentary (Moore & Engel, 1999) Cassandra Moore and Stephen Engel underline the importance of two further fMRI studies (one by Culham and colleagues, Culham et al., 1999), and the other by He and colleagues (He, Cohen, & Hu, 1998) that use behaviour variants on the basic effect to demonstrate particularly tight correlation of MT activity and the subjective perception of the effect. Both studies made use of the fact that the MAE lasts longer (after adaptation) if it is not elicited by the presentation of a stationary test pattern. In Culham’s study, the subject was kept in the dark after adaptation. Activity in MT decreased when in the dark, and returned during subsequent viewing of a stationary target that elicited the subjective impression of motion. In He’s study, the MAE was generated in only part of the visual field, and MT activity was elicited only when the stationary target was presented to the adapted portion of the field. To quote Moore and Engel, these two papers “... provide excellent examples of how neuroimaging techniques are being used to uncover the relationship between the mind and the brain” (Moore & Engel, 1999).

Another example of the use of behavioural data is in the work of Hans Breiter, Randy Gollub and colleagues in using fMRI to study the effects of cocaine (Breiter et al., 1997). As an aside, these studies are methodologically interesting because cocaine has systemic effects on the circulatory system and it was necessary to demonstrate, using an elegant experimental design and a variety of imaging strategies, that these circulatory effects only influenced the flow signal detected by fMRI, but not the BOLD signal (Gollub et al., 1998). However, the relevant point in the present context, analogous to the memory studies cited above, is that the imaging data were only interpretable by virtue of behavioural data that were being collected simultaneously. Subjects continuously rated their state of “craving”, “rush”, “high”, and “low” throughout a long (18 min) BOLD imaging sequence during which time they received an injection of either saline (a placebo) or cocaine. The wave forms generated by the behavioural responses to “craving” and “rush” were correlated with the imaging data to find regions that corresponded to these two subjective experiences.

### *11.2. Concerns: problems with local activation*

There is no shortage of things to be worried about in the domain of functional brain mapping. The theme of this section will be a collection of related concerns that all stem from the limitations of reporting data as a collection of activated voxels. The variations on this theme concern “thresholds”, the consequences of increasing statistical power of the tools, and the interpretation of the “most active” voxels across a small set of stimulus classes.

Consider, first, the question of thresholds. In a typical block design fMRI or PET experiment the data collected during one type of block are compared to the data collected during another type of block. A statistical test is applied at each voxel in space to decide when the difference between the distributions collected during the two types of blocks are statistically significant. A “map” is presented, typically showing anatomy in the background, with a coloured overlay indicating those voxels for which the statistic exceeds some threshold. How is that threshold determined?

Fig. 3 presents data for a simple experiment of this sort. A subject viewed a visual stimulus during the “On” blocks (10 s of counterphase flickering circular checkerboard, such as shown in Fig. 2(a)) alternating with a fixation point during the “Off” blocks (lasting 15 s). Fig. 3 shows five “activation maps” based on a statistical test comparing images collected during 2–3 min of alternating On and Off blocks. The slice of cortex passes through several visual areas.

The map in Fig. 3(d) suggests focal activity in lateral areas (MT/V5). The map in Fig. 3(a) suggests a broad region of activity, encompassing multiple visual areas. But the five maps are all based on exactly the same data. The only difference between them is the value of the threshold that has been set for the colour scale indicating “significant” activation. In this context, significant is not a restrictive term. *All* the activations shown in Fig. 3(a) are wildly significant. If I wanted to assert that flickering checkerboards were particularly good activators of MT/V5, I might choose to show Fig. 3(d). And I would be being honest and correct. Flickering checker-

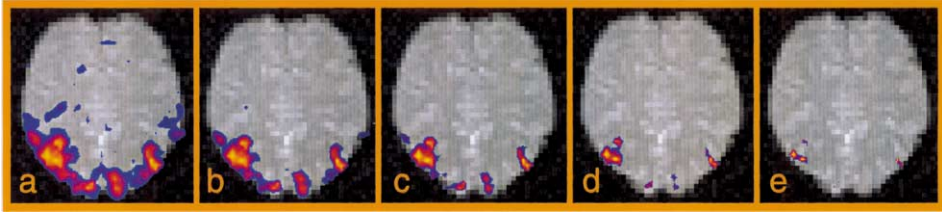


Fig. 3. This figure indicates the influence of the (sometimes arbitrarily chosen) threshold for statistical significance that can be used in making maps. The data were collected over a period of about 3 min, from one subject looking at a flickering checkerboard pattern for 10 s alternating with 15 s of a fixation point alone. (The stimulus pattern was the same as shown in Fig. 2(a), but the time course was different.) Each map of activation is based on the same functional data; and each map is based on the same statistical test computed on that data. The differences are based on the thresholds used to determine whether a given activated area will be shown in the map. In the image on the right the threshold is high; in the image on the left it is low. In all cases, however, these thresholds were highly significant, statistically. Note that the size, shape, and number of “activated” areas are dramatically changed by the choice of threshold.

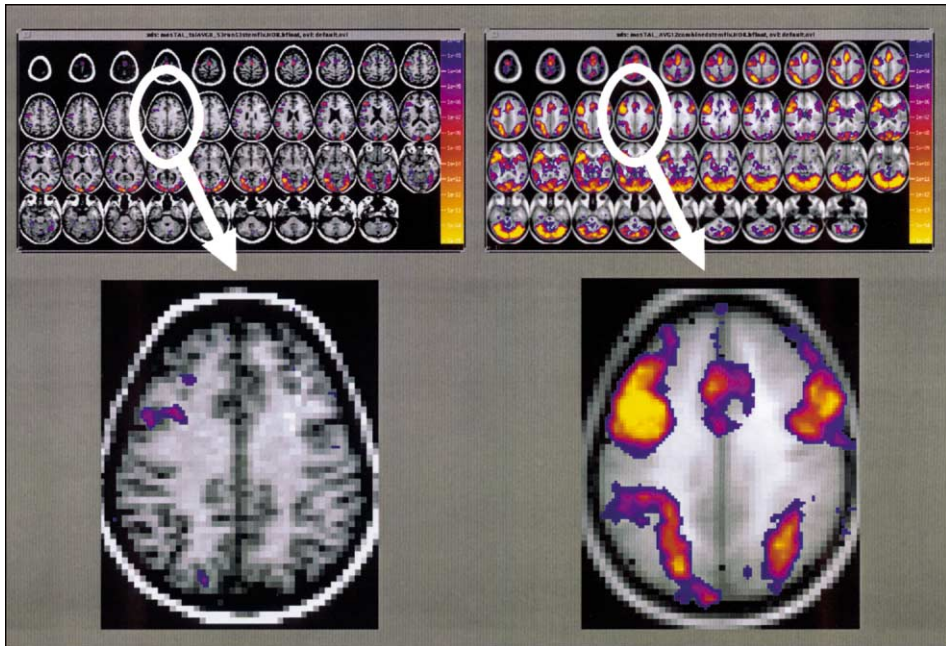


Fig. 4. Data from a verbal processing task, with the upper map showing slices across the entire brain, at different Talairach  $z$  levels, and the lower map showing an enlargement of one of those slices. The maps on the left show the activations based on data from one subject. The maps on the right show the activations based on data averaged over 12 subjects. The threshold for statistical significance is kept constant. See text for further discussion.

boards *are* particularly good activators of MT/V5. But if I wanted to assert that flickering checkerboards are excellent activators of many early visual processing areas in the occipital cortex, I might choose to show Fig. 3(a). And again, I would be being honest and correct.

The problem outlined above is just the tip of the conceptual iceberg. What are the relevant brain areas activated in a given task? The complete answer to this question must not be limited to the brain areas that happen to exceed some arbitrary, practical threshold for detection by our current (say 1.5 T) MRI machine. Suppose the same experiment could be performed on a 4 T machine. Would the same experiment and the same data analysis (using the same statistical threshold) yield more activated areas? The answer is almost certainly “Yes”.

This problem is likened to the classic question raised by Paul Meehl in the context of general experimental questions in psychology (Meehl, 1967). Meehl’s observation was simply that if psychological questions take the form “Will Group A differ from Group B by scoring statistically differently (either higher or lower) on some behavioural measure X?”, then as we increase the power of our statistical tests, the answer will almost certainly be Yes, *for any A, B, and X!* That is, while correlation between two presumptively equivalent groups on an unrelated task (e.g., Group A – persons with red hair; Group B – persons with brown hair; and the task X is IQ score) is likely to be insignificant when the number of subjects is modest (say,  $N = 20$  in each group), the story changes when  $N = 55,000$ . The reason is simply that even hair colour has some association with ethnicity, which might be associated with religious orientation, which might be associated with emphasis on education, etc. The associations are weak enough that they do not yield a significant relationship between the groups and the task when  $N$  is small, but they do when  $N$  is large. As a dramatic demonstration of this point, Meehl cites a study of 55,000 Minnesota high school seniors, for whom statistically significant correlations were found in 91% of pairwise comparisons among miscellaneous measures such as sex, college choice, club membership, mother’s education, dancing, interest in woodworking, birth order, religious preference, number of siblings, etc. These were not “spurious” correlations, but real associations that were detected because of the form of the question and the power of the test made possible by a very large  $N$ .

It is believed that there is a highly analogous problem lurking in the context of functional neuroimaging. The analogous concern applies to questions of the form, “Will area A in the cortex show a change in activity (an increase or decrease) in response to task X, compared to its response to task Y?” If our imaging system is powerful enough (it we go to 7 T; if we design more effective receiver coils for the MR scanner; if we use more subjects; if we collect data for a longer period of time), then the answer will almost always be Yes, for any A, X, and Y. Once we get past the peripheral sensory systems (i.e., once we have reached the thalamus), there are only about 5 synapses between any two neurones in the brain. It is likely that the activity in any one neurone (or collection of neurones, given the spatial resolution of our non-invasive imaging techniques) is going to influence almost any other neurone, albeit weakly. Data collected across multiple subjects on the same task give a hint of such a conclusion, in that the apparent area of activation increases as the number of

subjects increases, as long as the threshold for statistical significance is held constant. This is illustrated in Fig. 4, using data adapted from Ojemann et al. (1998).

There are two points to be taken from Fig. 4. The first is that many more brain areas are seen to be activated in the averaged data because the increase in number of subjects makes it more powerful in detecting statistically significant activations. The second point is that even for a region – such as the one in the upper left of the enlarged slice – that is seen to be active for a single subject, the size of the activated region is much greater in the averaged data. Some of this increase in the apparent size of activated areas could be due to the limitations of the Talairach system for spatial normalisation when averaging data across brains. However, as indicated in the relatively limited blurring of the anatomical images behind the activations, loss of resolution accompanying the averaging is much less than the increase in area of activation.<sup>5</sup>

Suppose, for the moment, that we are satisfied that we have measured the appropriate spatial extent of activation for a given stimulus. How do we report this data and interpret the meaning of the activated region? Is the relevant measure the most activated voxel, the centre-of-mass, the border, or the whole pattern of activity? This is not a rhetorical question – many studies in the literature report only the peaks or centres-of-mass of the activated areas.

Alumit Ishai and colleagues (Ishai, Ungerleider, Martin, Shouten, & Haxby, 1999) present data that indicate the importance of this limitation. Their study involved the visual presentation of three categories of objects: house, faces, and chairs. In one of their figures, they report the regions of the fusiform and temporal gyri that respond maximally to each of these stimulus classes. That is, they show broad areas for which there is statistically significant activation and the activation is strongest to one of these three stimuli, in comparison to the other two. If that were the only figure shown, it would lend itself to the natural – but misguided – interpretation that they had delineated the “face-area”, “chair area” and “house-area” of cortex. To their credit, the authors *also* show the entire activation pattern for each class alone. It is clear that the vast majority of voxels that are “maximally” responsive to one of these stimulus classes are also *statistically significantly active* for the other two as well. Thus, any sensible understanding of how these concepts are represented is likely to require the integration of many voxels, and not just a peak or centre-of-mass or collection of voxels that respond maximally to stimulus 1 compared with stimulus 2 and 3. Furthermore, there is no reason to think that other areas, which might fall below statistical significance for this particular experiment and this particular MR scanner, might not be contributing in important ways to the activation patterns that represent the brain’s response to these stimuli.

These concerns about thresholds and the extent of activation in response to a given stimulus are not limited to academic contexts. When functional MRI becomes a routine clinical tool, one of the dials that clinicians will undoubtedly have at their disposal will be a “threshold” adjustment (just as they have “brightness” and

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<sup>5</sup> Another possible interpretation of the increased area of activated regions is that the increase in sensitivity (gained by averaging across more subjects) permits the detection of small changes in hemodynamics farther from the activation site.

“contrast” adjustment knobs now). Clinical fMRI may use a standard set of activation paradigms and one could speculate that the way in which the patterns of detected activations change as the threshold is varied might be characteristic of specific disorders.

### *11.3. Integrating data: beyond local activation*

The issues raised in the preceding section are, for the most part, well understood by the brain mapping community. Indeed, one colleague suggested that studies limited to such simple “here it is activated, here it is not” analyses are hopefully a thing of the past. More specifically, there is an increasingly widespread understanding that cutting-edge experiments must use parametrically varied stimuli (e.g., Boynton et al., 1996; Morris et al., 1998; Sereno et al., 1995), multi-factorial design (e.g., Fletcher et al., 1995), and attempt to make use of the quantitative measures (e.g., percent activation) rather than purely qualitative measures (e.g., exceeds threshold) inherent in the data (e.g., Bandettini et al., 2000).

Notwithstanding my agreement with such sentiments, it is still the case that vast quantities of “here it is activated, here it is not” data will continue to be reported. The present section describes four approaches being taken by the brain mapping community to go beyond the limitations associated with such data. First, some of the attempts to make more of the raw data publicly available will be described. Second, one attempt at “meta-analysis” of a significant collection of this data will be described. Third, efforts to use spatial correlations across activated areas to obtain more comprehensible patterns from the data will be very briefly summarised. Finally, what is believed to be the necessary ultimate solution to the problem of integrating all this data – the creation and testing of functional models – will be mentioned.

There have been attempts to engage the brain mapping community in voluntary co-operation to support a standard database representation to facilitate public access to published (and possibly unpublished) functional neuroimaging data. The first major attempt was called “BrainMap” (<http://ric.uthscsa.edu/projects/brainmap.html>). One of the critical components of BrainMap was the requirement that all data (activated sites) were reported in the widely accepted, three-dimensional co-ordinate system (the Talairach system) that has become a standard. Additionally, investigators were required to describe their experimental procedures in sufficient detail to permit comparison and to facilitate computer searches. BrainMap was an ambitious project and a great deal was learned from the attempt, but many factors contributed to its being less than a rousing success. A new effort is now underway called the “National Functional MRI Data Center” (<http://www.fmridc.org>). Among other things, one intention of this group is to encourage journals to require that the raw data from functional neuroimaging experiments be submitted to them at the time of publication. Although this effort raised controversy ([http://www.psy.vanderbilt.edu/faculty/gauthier/fmridc/\\_letter.html](http://www.psy.vanderbilt.edu/faculty/gauthier/fmridc/_letter.html)), at least one journal does currently make this requirement. Having access to the raw data from studies is certainly one way to address the issue, raised above, of the limitation of reporting data based on only one (rather arbitrary) threshold.



There are many problems with attempting to create and use such a database. Some investigators do not think the Talairach co-ordinate system is the best way to represent the data, and several other systems are under development. Not every investigator is happy about making data public that might be mined for further publications of their own. However, I do not think that the fundamental problem with integrating the data from functional neuroimaging is related to databases, nor to the choice of co-ordinate system that is used to compare data across subjects, nor even to the uncooperativeness of individual investigators. Rather, the nature of the experiments that generates these data makes simple “database” integration extremely problematic, if not impossible. Brain mapping data are not like protein or DNA sequences. It is not the case that, once you have the data, the precise manner in which those data were collected is irrelevant. In a brain imaging study each detail of the experiment – from the exact wording of the instructions to the subject, to the precise characterisation of the stimuli – may have a significant impact on the meaning and interpretation of the resulting data. Thus, each individual brain activation is the result of an experimental design and procedure whose essence is not easily captured in a database. Words can be written to describe the procedure, but an entirely different level of “artificial intelligence” would be needed to automatically integrate such descriptions – a level of intelligence that our current computers systems are famous for not possessing.

Notwithstanding the past and ongoing problems associated with creating a standardised database of functional neuroimaging data, the fact that most published reports now include a representation of local activations using Talairach co-ordinates facilitates the attempt to do meta-analyses of these data by hand. Perhaps the most ambitious such attempt has been by Cabeza and Nyberg. In 1997 (with 73 PET studies) and again in 2000 (with 275 PET and fMRI studies), these investigators presented meta-analyses of a large collection of cognitive experiments (Cabeza & Nyberg, 1997, 2000). They have performed a Herculean task in accumulating and tabulating the data from many individual experiments. Talairach co-ordinates, Brodmann areas, and the names of the various cortical lobes and subcortical structures are cross-indexed in the large tables for many activation foci across these tasks. Surface projections of the collected activations for a given general category (“Attention”, “Perception”, “Imagery”, “Language”, “Working Memory”, etc.) are presented for the left and right cortical hemispheres, in both lateral and midline views, as well as a subcortical slice and a slice through the cerebellum.

And yet, when all is said and done, about the most that can be gleaned from these pictures is that, for instance, tasks involving language tend to elicit activation foci on the left hemisphere more than the right, and tend to be localised on the temporal lobe and Broca’s area on the frontal lobe. But this information was already clear in Fig. 1, from 1957! The problem is not with the data. The individual experiments (in the collection of 73 or 275) are designed to address specific, often interesting questions. And the problem is not with Cabeza and Nyberg’s tabulation or presentation, which is thorough and clear. The problem is that this kind of collecting of data does not represent an intellectual integration.

I believe that the only way to achieve a true integration of these data depends upon the development of neuropsychological models and theories that detail functional systems in testable ways. This notion will be elaborated at the end of this section, but before that, it is important to describe a kind of intermediate step – one that is of increasing interest in the brain mapping community, and may be of critical importance in making the leap to truly integrative theories.

Several methods have been developed to make use of spatial covariances inherent in the raw data from PET and fMRI, and in the activation maps generated by a collection of experiments. One class of approaches is completely data-driven – it makes no assumptions about underlying neural or data structures. Instead, patterns of spatial covariance and spatial correlation are extracted from the data using a collection of multivariate tools (partial least squares, principle component analysis, etc.) that permit the automatic detection of relationships within the imaging data and between the imaging and behavioural data or paradigm. Another kind of approach – called “structural equation modelling” – seeks to quantify the connection strengths between disparate areas in the brain using a combination of covariance analysis and assumptions about the underlying physiological connections between brain areas. In a general description of these techniques, with particular application to questions of memory, McIntosh (1999) summarises the basic concepts, strengths and weaknesses. He points out that although structural equation modelling depends upon assumptions about possible connections between brain areas, it is capable of detecting changes in brain interactions that would not be detectable through activation analyses alone.

These analyses may supply useful information. On the other hand, it is also possible that they may generate more (essentially descriptive) data of the sort that Cabeza and Nyberg attempted to summarise. Collections of possible connection strengths between brain regions, by themselves, are no more defining of testable theories than the activated sites alone. Similarly, the extraction of distributed patterns of activation might suggest an interesting theory, but the data, alone, do not. Thus, these data may be helpful clues to theory building, but the process of going from correlational data to neuropsychological theory is neither obvious nor automatic.

The only path that I can see toward conceptual integration of this data on a broad scale requires the kind of cognitive and neural models that have often, heretofore, been insufficiently testable (and consequently of less centrality to psychology and systems neuroscience than they might be). Books (e.g., Kosslyn & Andersen, 1992) and a recent special journal issue (Jennings & Aamodt, 2000) have been devoted to this topic. A wide assortment of opinions exists, from the perennial favourite, “I cannot think of one [theory] that has made a really significant contribution to neurobiology.” (Stevens, 2000, p. 1177), to the opposite extreme, “...what most neuroscientists want to know about the brain is the model ... The brain as an electrical system or a chemical system is simply not the point” (Mel, 2000, p. 1183). It is not impossible to take the position that both extremes are correct, and to argue for more efforts in the direction of creating integrative (explaining a substantial range of data) but testable theories.

Some researchers are starting to guide their neuroimaging studies with tightly coupled connection to moderately detailed models of cortical systems, as well as evaluating substantial bodies of imaging data in terms of particular models (e.g., Botvinick, Braver, Barch, Carter, & Cohen, in press; Carter et al., 1998). The history of modelling's impact (or lack thereof) on the research enterprise of psychology is not one that is free from bumps, and it is not likely to be a simple path in the future. But alternatives are hard to find. And the challenge that all these data represent for the cognitive neuroscience and neuroimaging communities is clear.

## 12. Closing

My pre-doctoral education included a broad spectrum of psychology, physics, electrical engineering and mathematics. My doctoral training was in visual psychophysics. My exposure to neuroscience and brains during those years was limited to single-cell recording studies. Why did I start looking at brains and brain function at the systemic level in 1992? Why am I still at it after 8 years? Why am I excited about the future of functional brain imaging and cognitive neuroscience?

The answer, in a word, is technology; or perhaps more fully, the likelihood of a productive synergy between the developing technologies and the tools of experimental psychology. Functional MRI was the first technology that promised non-invasive, reasonably high spatial resolution, volumetric images of brain activity in normal human subjects, with the opportunity to do repeated studies on the same subject, including healthy children. To be sure, there were many questions about the foundation of this technology for functional brain imaging, and many practical limitations to its use in this context in 1992. Nonetheless, it seemed to me that there was a good chance that these limitations would be temporary, and, more importantly, that the technology was in its infancy with regard to functional brain imaging. This has proved to be the case. There is no longer any question that functional MRI is generally accepted as a cutting-edge tool for cognitive neuroscience, as the articles in the remainder of this special issue of *Acta Psychologica* demonstrate.

The editors asked us to consider the following three questions. (1) What type of questions can now be addressed that could not be addressed by traditional psychonomics? Clearly, the answer is that the new tools allow us to address questions of neuropsychology rather than purely behavioural psychology. (2) What contributions can psychonomics make to the field of cognitive neurosciences? In my opinion some of the examples cited above, in which clever behavioural tasks are joined with neuroimaging techniques, exemplify the kinds of contributions psychologists can make to cognitive neuroscience. One obligation, in order to be a successful player in this game, is to become much more sophisticated about brain structure and function in the design of experiments than psychologists normally are. There is no getting away from the fact that these are brain-based tools. (3) Are neuroimaging techniques capable of providing more insights than just localisation of well-known cognitive functions? The answer to this question must be Yes, at least in principle. Integration of volumetric (fMRI) and real-time neural (EEG/MEG) data may yield detailed

information about underlying networks in a way that goes far beyond mere “localisation of well-known cognitive functions”. Some model-based experimentation and theorising is, by definition, an attempt to go beyond questions of localisation. Finally, as indicated in the comments above about broad meta-analyses of cognitive neuroimaging studies, it will be essential, if we are to have any hope of integrating these data, to develop more tightly coupled, refined and general network models of brain function. I cannot imagine any other way to integrate that data, but it will not be an easy task. (4) Another question was presented in the Introduction: Do the new discoveries about human brain function based on neuroimaging experiments really teach us things that are relevant for the study and understanding of behaviour? That is a question which you must answer. My own impression is that, at present, the overwhelming thrust of these data are toward understanding brain organisation, rather than human behaviour. Of course, we assume that when brain organisation is sufficiently well understood, it will lead to increases in our understanding of behaviour. But I do not think, as yet, there is a great deal of progress in that direction.

This accounts for the past and the present. What about the future? I have expressed my theoretical concerns above, but these are tempered by a collection of exciting developments on the technological front. In the context of MRI, there have been two developments in the recent past that would be of great importance if they come to fruition. One is the use of diffusion tensor imaging (e.g., Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Makris et al., 1997; Tuch, Wedeen, Dale, George, & Belliveau, 1999) to detect the orientation of white matter fibre bundles, despite the fact that the underlying axons are much too small to be imaged by themselves. Early reports of this idea have been followed up by several laboratories. While there is still a long way to go, the motivation is as follows. We have surprisingly limited knowledge of the connecting pathways for the frontal lobe in man. The techniques used to trace connections in monkeys require the sacrifice of the animal a few days after injecting a labelled tracer. While many of the cortical connections are similar between man and monkey, it is precisely the parts of the brain that are so different that makes studying people important, and the frontal cortical connections are at the top of that list. MRI can be used to detect the orientation of fibre bundles by detecting the diffusion of water near those bundles. Water will diffuse more easily along the direction of the axons than across the axons. MRI can be used to detect this asymmetry of diffusion, and the resulting information may be of use in understanding various disorders (e.g., dyslexia; Kingberg et al., 2000). Better knowledge of white matter connections can only help in the analyses and modelling of all functional neuroimaging data.

A much more speculative idea is to detect electrical activity in the axons. The physical principle is relatively straightforward. When an action potential travels down an axon a current is generated. That current creates a tiny magnetic field, which, in the presence of the large external field, induces a physical force on the axons. That force would cause a small movement in the axons and that movement may cause changes in some MR signals that could be detected. One laboratory (Song & Takahashi, 2000) has suggested that such an effect has been seen, but my impression of the response of the physics community is that other explanations for the

data are possible. No one is saying that this is “cold fusion” – i.e., the underlying physical effect is plausible – but it is still highly speculative. On the other hand, this is the kind of physical effect that will be easier to detect as we move to stronger magnets.

The third arena for speculation is optical imaging. At first glance, optical imaging seems like an implausible approach because of the severe degradation of the light as it passes through the skull and other tissue (twice!) before being collected. But the physicists involved in this research are taking a three-pronged approach. First, it is reasonable clear that images indicating cerebral circulation and oxygenation state are possible to obtain optically. The instrumentation for these will be relatively inexpensive (orders of magnitude less expensive than MRI or PET), light and portable – probably usable at the bedside. The next step, to get tomographic images of some kind from this sort of data (again based on blood oxygenation), is an ongoing research project. But it is the third step – using broad band light or pulsed light to get at spectroscopy – that may yield a different level of information. There are known to be optical signal changes due to neural activity (rather than the indirect blood changes), and these will have temporal resolution comparable to EEG and MEG. The exciting question for optical neuroimaging is whether it will be possible to detect these changes optically and non-invasively (Chen, Perelman, Zhang, Dasari, & Feld, 2000).

It seems clear, today, that some phenomena reported by laboratories conducting fMRI-based research can only be seen at higher field (3 and 4 T). It may be that the 7 and 8 T whole body magnets now being used at a few selected sites, the integration of high temporal resolution electrical methods with volumetric imaging data, and the development of the largely unexplored possibilities of optical imaging, will open genuinely new technological windows on the function of the human brain. Currently the most active area that is at the boundary between “present” and “future” work is the integration of high temporal resolution electrical signals (EEG and MEG) with anatomical and functional information supplied largely by MRI. Will these advances in brain mapping lead to deeper understanding and the development of useful models of behaviour at the psychological level? There is no guarantee, but a lot of people are betting a lot of research money and their own research time that the answer will be “yes”.

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